



# *The American Journal of* DIGESTIVE DISEASES

*The Official Publication of*  
THE AMERICAN GASTRO-ENTEROLOGICAL ASSOCIATION

## CONTRIBUTIONS

|   | <i>Page</i> |
|---|-------------|
| A CLINICAL AND LABORATORY STUDY OF PLASMA LIPIDS IN OBSTRUCTIVE JAUNDICE AND SEVERAL TYPES OF HEPATIC DISEASE— <i>Charles A. Jones, M.D., D.Sc. (Med.)</i> - - - - -  | 1           |
| A COMPARATIVE EVALUATION OF THE NEWER LIVER FUNCTION TESTS. (COMPARISON OF THE INTRAVENOUS HIPURIC ACID TEST, THE CEPHALIN-CHOLESTEROL FLOCCULATION TEST, THE COLLOIDAL GOLD TEST AND A SERIAL BROMSULPHTHALEIN TEST WITH THE ORAL HIPURIC ACID TEST AND THE ROSENTHAL BROMSULPHTHALEIN TEST)— <i>John G. Mateer, M.D., James I. Baltz, M.D., Donald F. Marion, M.D. and Robert A. Hollands, M.D.</i> - - - - - | 13          |
| THE GENESIS OF PELLAGRA, PERNICIOUS ANEMIA AND SPRUE— <i>Seale Harris, M.D. and Seale Harris, Jr., M.D.</i> - - -   | 29          |
| A STUDY OF THE SPHINCTER OF ODDI IN THE HUMAN AND IN THE DOG— <i>H. Neecheles, M.D., Ph.D. and D. D. Kozoll, M.D.</i>   | 36          |
| THE EFFECT OF FOOD UPON THE SPHINCTER OF ODDI IN HUMAN SUBJECTS— <i>George S. Bergh</i> - - - - -   | 10          |
| PORPHYRINURIA IN THE AGED— <i>Henry A. Rafsky, M.D., F.A.C.P. and Bernard Newman, B.S., Ch.E.</i> - - - - -   | 43          |
| LYMPHOSARCOMA CAUSING OBSTRUCTION AT THE DUODENOJEJUNAL ANGLE: REPORT OF CASE— <i>Hendrik J. Srien, M.D. and Andrew B. Rivers, M.D.</i> - - - - -   | 45          |
| EDITORIAL:—   |             |
| SOME OF GREAT BRITAIN'S NUTRITIONAL PROBLEMS DURING THIS WAR - - - - -  | 47          |
| ABSTRACTS OF CURRENT LITERATURE - - - - -   | 48          |
| BOOK REVIEWS:—  |             |
| DARK LEGEND. A STUDY IN MURDER— <i>Frederic Wertham</i> - - - - -   | 28          |
| MAGIC IN A BOTTLE— <i>Milton Silverman</i> - - - - -  | 30          |
| BORN THAT WAY— <i>Earl R. Carlson, M.D.</i> - - - - -   | 30          |
| FEEDING OUR OLD FASHIONED CHILDREN— <i>C. Anderson Aldrich and Mary M. Aldrich</i> - - - - -  | 30          |





S. M. MEDICAL COLLEGE,  
LIBRARY,

J. R. No... 4.7.41

Date... 1.7... 9-64

# The Problem

## OF NUTRITION IN GERIATRICS

The declining physical activity of senescence has created in the minds of many aged persons the erroneous belief that dietary curtailment is desirable. Yet, modern authorities assert that nutritional requirements, with the exception of caloric fuel value, do not decrease, and their satisfaction is necessary if vigor, good health, and normal freedom from infectious disease is to be maintained.

The one-sided, usually inadequate diet of many aged persons can be readily balanced with New Improved Ovaltine. This delicious food drink provides nutrients likely to be lacking, and supplies

them in easily assimilated form. Ovaltine puts little tax on the digestive apparatus; its pleasing palatable taste rarely loses its appeal.

Three daily servings (1½ oz.) of New Improved Ovaltine provides:

|                        | Dry Ovaltine  | Ovaltine with milk* |
|------------------------|---------------|---------------------|
| PROTEIN                | 6.00 Gm.      | 30.00 Gm.           |
| CARBOHYDRATE           | 30.00 Gm.     | 65.00 Gm.           |
| FAT                    | 3.15 Gm.      | 31.95 Gm.           |
| CALCIUM                | 0.25 Gm.      | 1.05 Gm.            |
| PHOSPHORUS             | 0.25 Gm.      | 0.903 Gm.           |
| IRON                   | 10.5 mg.      | 11.9 mg.            |
| COPPER                 | 0.5 mg.       | 0.5 mg.             |
| VITAMIN A              | 1500 U.S.P.U. | 2953 U.S.P.U.       |
| VITAMIN D              | 405 U.S.P.U.  | 432 U.S.P.U.        |
| VITAMIN B <sub>1</sub> | 170 U.S.P.U.  | 302 U.S.P.U.        |
| RIBOFLAVIN             | 0.25 mg.      | 1.28 mg.            |

\*Each serving made with 8 oz. milk; based on average reported values for milk.



NEW IMPROVED

# Ovaltine

2 KINDS—PLAIN AND CHOCOLATE FLAVORED  
Ovaltine now comes in 2 forms—plain, and sweet chocolate flavored. Serving for serving, they are virtually identical in nutritional value.

Physicians are invited to send for a supply of individual servings of New Improved Ovaltine. The Wander Company, 360 North Michigan Avenue, Chicago, Illinois.

# *The American Journal of*

# DIGESTIVE DISEASES

The Official Publication of  
THE AMERICAN GASTRO-ENTEROLOGICAL ASSOCIATION

## CONTRIBUTIONS

|  | Page |
|--|------|
| GALL BLADDER DYSPEPSIA— <i>Rollin H. Moser, M.D., Bernard D. Rosenak, M.D. and Robert J. Hasterlik, M.D.</i> - - -   | 49   |
| THE PROBLEM OF COMMON DUCT STONES: FURTHER EXPERIENCE WITH AN INSTRUMENT FOR VISUALIZING THE INTERIOR OF THE COMMON DUCT AT OPERATION— <i>Monroe A. McIver, M.D.</i> - - -       | 52   |
| LIPOPHAGIC GRANULOMATOSIS OF THE ENTERIC TRACT— <i>Seaton Sailer, M.D. and R. J. McGann, M.D.</i> - - -  | 55   |
| ILEOCOLOSTOMY WITH EXCLUSION FOR NON-SPECIFIC ILEITIS— <i>Ralph Colp, M.D., John Garlock, M.D. and Leon Ginzburg, M.D.</i> - - -   | 64   |
| A CLINICAL STUDY OF THE SECRETIN TEST— <i>H. M. Pollard, M.D., Lila Miller, Ph.D. and W. A. Brewer, B.A.</i> - - -   | 68   |
| FUNCTIONAL DISTURBANCE OF THE SMALL INTESTINE IN CHRONIC IDIOPATHIC ULCERATIVE COLITIS— <i>Kendall A. Elsom, Francis G. Dickey and Francis W. Chornock</i> - - -                 | 74   |
| MOVEMENTS OF THE PANCREAS— <i>C. Abbott Beling, M.D., M.Sc.D., Charles Frederick Baker, M.D. and W. James Marquis, M.D.</i> - - -  | 76   |
| A CASE OF ATROPHIC GASTRITIS SUCCESSFULLY TREATED WITH LIVER-STOMACH CONCENTRATE— <i>Ralph U. Leser, M.D. and Robert J. Hasterlik, M.D.</i> - - -                                | 78   |
| HALITOSIS, TRUE AND FALSE— <i>Rudolph Drosd, M.D. and Burrill B. Crohn, M.D.</i> - - -   | 79   |
| THE EFFECT OF ACUTE ALCOHOLIC INTOXICATION ON HEPATIC FUNCTION— <i>J. M. Beazell, Ph.D., M.D., A. L. Berman, M.B., Ph.D., V. H. Hough, B.A. and A. C. Ivy, Ph.D., M.D.</i> - - - | 82   |
| CONGRATULATIONS TO DR. MAX EINHORN ON HIS EIGHTIETH BIRTHDAY— <i>Hyman I. Goldstein, M.D.</i> - - -  | 85   |
| ABSTRACTS OF CURRENT LITERATURE - - -  | 86   |



## FROM WHATEVER ANGLE YOU LOOK AT IT

Looking at Alka-Zane from every viewpoint of clinical application, one can readily see how well it fills the role of a well-balanced systemic alkalizer.

Sodium, potassium, calcium, and magnesium in Alka-Zane are supplied in the readily assimilable form of citrates, carbonates, and phosphates. And it is worth noting that one dose of Alka-Zane affords as much basic calcium as do 12 grains of calcium lactate or 18 grains of calcium gluconate.

Alka-Zane makes a zestful and refreshing drink. Its pleasing taste is especially appreciated when palatability counts most, as in the "morning sickness" of pregnancy. Why not observe the usefulness of Alka-Zane in this, as well as other conditions requiring an alkalizer, by giving it a trial? We shall gladly send a supply if you will write a request on your letterhead, addressing it to the Department of Professional Service. Alka-Zane is available in bottles of 1½, 4 and 8 ounces.

# ALKA-ZANE

WILLIAM R. WARNER & COMPANY, INC. • 113 West 18th Street, New York City

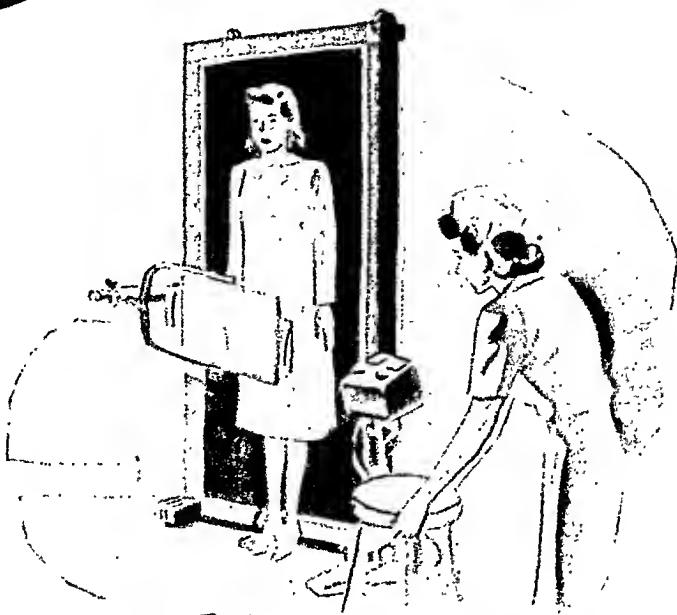
# *The American Journal of* DIGESTIVE DISEASES

*The Official Publication of*  
THE AMERICAN GASTRO-ENTEROLOGICAL ASSOCIATION

Cambridge City Hospital

## CONTRIBUTIONS

|   | Page |
|---|------|
| PROGNOSIS OF REGIONAL ENTERITIS— <i>Philip W. Brown, M.D. and Charles J. Donald, Jr., M.D.</i> - - - - -  | 87   |
| ULCERATIVE COLITIS—AN ALLERGIC PHENOMENON— <i>Albert F. R. Andresen, M.D., F.A.C.P.</i> - - - - -   | 91   |
| THE ENZYMATIC ACTIVITY OF DUODENAL JUICE AND BLOOD SERUM OF PATIENTS WITH ATROPHY OF THE GASTRIC MUCOSA<br>— <i>A. M. Serby, M.D. and Frederick Reich, Ph.D.</i> - - - - -    | 98   |
| FREE TYROSIN IN THE BLOOD FILTRATE AS AN INDICATION OF LIVER DISEASE— <i>I. R. Jankelson, M.D.</i> - - - - -  | 99   |
| A STUDY OF THE EXCRETION OF BROMSULPHTHALEIN IN THE BILE— <i>C. W. Wirts, Jr., M.D. and A. Cantarow, M.D.</i> - - -   | 101  |
| LIMITATIONS IN THE USE OF COLOR INDICATORS IN GASTRIC ANALYSIS— <i>J. Edward Berk, M.D., M.Sc. (Med.), J. Earl Thomas, M.D. and Martin E. Rehfuess, M.D.</i> - - - - -        | 106  |
| THE EXCRETION OF NEUTRAL RED BY THE GASTRIC MUCOSA AS VISUALIZED GASTROSCOPICALLY— <i>Henry H. Lerner, M.D., Leonard Asher, M.D. and Katherine Andrews, M.D.</i> - - - - -    | 109  |
| THE PROGNOSTIC SIGNIFICANCE OF THE BLOOD UREA NITROGEN FOLLOWING HEMATEMESIS OR MELENA— <i>Leon Schiff, M.D., Richard J. Stevens, M.D. and Harold K. Moss, M.D.</i> - - - - - | 110  |
| EDITORIALS:—  |      |
| CARCINOMA OF THE PANCREAS - - - - -   | 113  |
| NIGHT BLINDNESS IN SOLDIERS: A SIGN OF PSYCHONEUROSIS RATHER THAN OF AVITAMINOSIS - - - - -   | 114  |
| STUDIES ON INTESTINAL DIGESTION WITH A NEW TECHNIC - - - - -  | 114  |
| REPORT OF THE COMMITTEE ON MILITARY PREPAREDNESS— <i>John L. Kantor</i> - - - - -   | 114  |
| THE AMERICAN GASTROSCOPIC CLUB— <i>Joseph B. Kirsner</i> - - - - -  | 10   |
| ABSTRACTS OF CURRENT LITERATURE - - - - -   | 11   |



## GASTRO-INTESTINAL AFFECTIONS

# *and Adequate Nutrition*

The low-fiber, low-residue diet so frequently called for in the treatment of gastro-intestinal affections need not threaten the nutritional state. Through the use of New Improved Ovaltine, the daily protein, mineral, and vitamin intake can be appreciably augmented.

Virtually devoid of undigestible residue, this delicious food drink is mechanically and chemically bland. Yet it is attractive to the palate and is taken with relish by most patients. Ovaltine often

balances the nutritionally inadequate diet necessitated by gastric and intestinal derangements.

Three daily servings (1 1/4 oz.) of New Improved Ovaltine provide:

|                                  | Dry Ovaltine  | Ovaltine with milk* |
|----------------------------------|---------------|---------------------|
| PROTEIN . . .                    | 6.00 Gm.      | 31.20 Gm.           |
| CARBOHYDRATE . . .               | 33.00 Gm.     | 55.00 Gm.           |
| FAT . . . . .                    | 3.15 Gm.      | 31.95 Gm.           |
| CALCIUM . . . . .                | 0.25 Gm.      | 1.05 Gm.            |
| PHOSPHORUS . . . . .             | 0.25 Gm.      | 0.93 Gm.            |
| IRON . . . . .                   | 10.5 mg.      | 11.9 mg.            |
| COPPER . . . . .                 | 0.5 mg.       | 0.5 mg.             |
| VITAMIN A . . . . .              | 1500 U.S.P.U. | 2953 U.S.P.U.       |
| VITAMIN D . . . . .              | 405 U.S.P.U.  | 432 U.S.P.U.        |
| VITAMIN B <sub>1</sub> . . . . . | 170 U.S.P.U.  | 132 U.S.P.U.        |
| RIBOFLAVIN . . . . .             | 0.75 mg.      | 1.28 mg.            |

\*Each serving made with 1/2 cup milk, based on average reported value for milk.



NEW IMPROVED

# Ovaltine

2 KINDS—PLAIN AND CHOCOLATE FLAVORED

Ovaltine now comes in 2 forms—plain, and sweet chocolate flavored. Serving for serving, they are virtually identical in nutritional value.

Physicians are invited to send for a supply of individual servings of New Improved Ovaltine. The Wander Company, 360 North Michigan Avenue, Chicago, Illinois.

# *The American Journal of* DIGESTIVE DISEASES

*The Official Publication of*  
THE AMERICAN GASTRO-ENTEROLOGICAL ASSOCIATION

## CONTRIBUTIONS

|   | <i>Page</i> |
|---|-------------|
| PORTAL CIRRHOSIS WITH ASCITES: AN ANALYSIS OF 200 CASES WITH SPECIAL REFERENCE TO PROGNOSIS AND TREATMENT<br>— <i>Ralph G. Fleming, M.D. and Albert M. Snell, M.D.</i> - - - - -  | 115         |
| TWO CASES OF DOUBLE GALL BLADDER— <i>Meyer Golob, M.D. and John L. Kantor, M.D.</i> - - - - -   | 120         |
| A SELF REGULATORY DUODENAL MECHANISM FOR GASTRIC ACID CONTROL AND AN EXPLANATION FOR THE PATHOLOGIC<br>GASTRIC PHYSIOLOGY IN UNCOMPLICATED DUODENAL ULCER— <i>Harry Shay, M.D., J. Gershon-Cohen, M.D., D.Sc.</i><br>( <i>Med.</i> ) and <i>Samuel S. Fels, LL.D.</i> - - - - - | 124         |
| THE SERUM COAGULATION REACTION: ITS CLINICAL SIGNIFICANCE— <i>Manfred Kraemer, M.D.</i> - - - - -   | 129         |
| THE USE OF CONCENTRATED AND PURIFIED ANTITOXIC B. COLI SERUM IN THE TREATMENT OF INDETERMINATE ULCERATIVE<br>COLITIS— <i>Asher Winkelstein, M.D. and Gregory Shwartzman, M.D.</i> - - - - -   | 133         |
| THE RELATIONSHIP BETWEEN GASTRIC MOTILITY, MUSCULAR TWITCHING DURING SLEEP AND DREAMING— <i>H. B. McGlade</i>   | 137         |
| PROCTOSCOPIC CINEMATOGRAPHY— <i>J. F. Pessel, M.D., Jay M. Garner, M.D. and J. F. Nesselrod, M.D.</i> - - - - -   | 140         |
| THE SIGNIFICANCE OF DOSAGE AND TIME FACTORS ON THE VALUE OF THE BROMSULPHTHALEIN TEST FOR LIVER FUNCTION<br>— <i>John D. Helm, M.D. and Thomas E. Machella, M.D.</i> - - - - -  | 141         |
| THE TREATMENT OF ANORECTAL INFECTIONS WITH SUPPOSITORIES CONTAINING SULFANILAMIDE AND LOCAL ANESTHETIC:<br>PRELIMINARY REPORT— <i>Harold Laufman, M.D. and Mortimer Diamond, M.D.</i> - - - - -   | 144         |
| THE AMERICAN GASTROSCOPIC CLUB - - - - -  | 146         |
| ABSTRACTS OF CURRENT LITERATURE - - - - -   | 146         |

# The Newer Concepts of Meat in Nutrition

## Meat . . . in the Management of Enteric Disease

IN THE dietary management of many intestinal disturbances such as colitis, the dysenteries, and acute catarrhal enteritis a low-fiber, low-residue diet is indicated. Hence many foods ordinarily depended on for vitamins and minerals must be eliminated because of their content of indigestible cellulose which proves irritating to the hypersensitive intestinal tract. Easily digestible, low-fiber foods must carry the burden of satisfying nutritional requirements. Furthermore, since the need for thiamine and other B complex vitamins is increased in these conditions, the dietary must be especially rich in these vitamins.

According to Donald and Brown,<sup>2</sup>

protein derived chiefly from red meats, liver, kidney, sweetbreads, and lean pork is the most important food for the patient afflicted with ulcerative disease of the colon. They concluded from their investigation that the prognosis is greatly improved by a high protein diet.

Because meat and meat specialties (kidney, liver, and sweetbreads) contain little or no irritating fiber, and are almost totally digestible, they are pre-eminent in low-residue diets as food sources of biologically adequate proteins, the essential B vitamins and the minerals iron, copper, and phosphorus.

<sup>2</sup>Donald, C. L., Jr., and Brown, P. W.: *Enteric Colitis*. Am. J. Digest. Dis. 7:231 (Dec) 1942.

*The Seal of Acceptance denotes that the statements made in this advertisement are acceptable to the Council on Foods and Nutrition of the American Medical Association.*



*American Meat Institute*  
CHICAGO

# *The American Journal of*

# DIGESTIVE DISEASES

*The Official Publication of*

THE AMERICAN GASTRO-ENTEROLOGICAL ASSOCIATION

## CONTRIBUTIONS

|   | Page |
|---|------|
| FAMILIAL OCCURRENCE OF CHRONIC ULCERATIVE COLITIS (THROMBO-ULCERATIVE COLITIS): REPORT OF CASES— <i>Raymond J. Jackman, M.D. and J. Arnold Bargen, M.D.</i> - - - - -                                 | 147  |
| THE GASTRIC MUCOSA IN BENIGN ADENOMAS— <i>Rudolf Schindler, M.D.</i> - - - - -  | 149  |
| BLEEDING PEPTIC ULCER. A CLINICAL STUDY WITH SPECIAL REFERENCE TO THE MEULENGRACHT REGIMEN— <i>N. W. Chaikin, M.D. and Oscar Tannenbaum, M.D.</i> - - - - -   | 150  |
| INVESTIGATION OF THE RELATIONSHIP BETWEEN BLOOD SUGAR AND GENERAL COMPLAINTS FOLLOWING SUBTOTAL GASTRIC RESECTION— <i>A. Schwartz, M.D., I. Reingold, M.D. and H. Necheles, M.D., Ph.D.</i> - - - - - | 151  |
| OCCULT BLOOD WITH A NOTE ON THE USE OF CARMINE FOR THE MARKING OF STOOLS— <i>M. Kirschen, M.D., H. Sorter, M.D. and H. Necheles, M.D., Ph.D.</i> - - - - -  | 154  |
| STUDIES ON OLD AGE. V. ACTIVE PANCREATIC SECRETION IN THE AGED— <i>H. Necheles, M.D., Ph.D., F. Plotke, M.D. and Jacob Meyer, M.D.</i> - - - - -  | 157  |
| STUDIES ON OLD AGE. VI. BLOOD ENZYMES IN THE AGED— <i>Jacob Meyer, M.D., H. Sorter, M.D. and H. Necheles, M.D., Ph.D.</i> - - - - -   | 160  |
| THE EFFECT OF MAGNESIUM SULPHATE UPON THE SPHINCTER OF ODDI OF MAN— <i>George S. Bergh, M.D. and John A. Layne, M.D.</i> - - - - -  | 162  |
| IS THE BENEFICIAL EFFECT OF URINE EXTRACTS ON MANN-WILLIAMSON ULCERS DUE TO THE GASTRIC SECRETORY DEPRESSANT IN URINE?— <i>David J. Sandweiss, M.D. and M. H. F. Friedman, Ph.D.</i> - - - - -        | 166  |
| ON THE EXPLANATION OF THE UROBILINURIA PRESENT IN CASES OF HEMATOMA AND A NEW VIEW ON THE ORIGIN OF UROBILINOGEN FROM BILE PIGMENT— <i>J. W. G. Ten Bokkel Hinnink, M.D.</i> - - - - -                | 168  |
| PROLONGATION OF SURVIVAL TIME IN MANN-WILLIAMSON DOGS BY SUPPLEMENTING DIETS WITH AMINO ACIDS— <i>David Shoch, M.S. and Samuel J. Fogelson, M.D.</i> - - - - -  | 173  |
| ACUTE AND CHRONIC CECAL VOLVULUS— <i>Donovan C. Browne, M.D. and Gordon McHardy, M.D.</i> - - - - -   | 177  |
| PROGRAM OF THE FORTY-FIFTH ANNUAL MEETING OF THE AMERICAN GASTRO-ENTEROLOGICAL ASSOCIATION AT ATLANTIC CITY, NEW JERSEY - - - - -   | IX   |
| NOTICE TO MEMBERS OF AMERICAN GASTRO-ENTEROLOGICAL ASSOCIATION FROM ADVISORY COMMITTEE ON GASTRO-ENTEROLOGY OF THE AMERICAN BOARD OF INTERNAL MEDICINE - - - - -                                      | X    |
| ABSTRACTS OF CURRENT LITERATURE - - - - -   | XI   |





# IN THE MAINTENANCE OF *Nutrition* DURING FEBRILE DISEASE

The intensified metabolic processes of febrile periods increase the need for most specific nutrients and for calories. But the patient afflicted with an infectious process usually finds it difficult to consume the required amounts of food.

Rich in many food essentials, New Improved Ovaltine is an effective means of bolstering depleted carbohydrate, protein, mineral, and vitamin stores. This delicious food drink appeals to virtually all patients, thus helps with the problem of maintaining the nutritional state. Its easy digestibility

and its freedom from residue make Ovaltine especially valuable, even in the presence of gastrointestinal disease.

Three daily servings (1½ oz.) of New Improved Ovaltine provides:

|                                  | Dry<br>Ovaltine | Ovaltine<br>with milk* |
|----------------------------------|-----------------|------------------------|
| PROTEIN . . . . .                | 6.00 Gm.        | 31.20 Gm.              |
| CARBOHYDRATE . . . . .           | 30.00 Gm.       | 66.00 Gm.              |
| FAT . . . . .                    | 3.15 Gm.        | 31.95 Gm.              |
| CALCIUM . . . . .                | 0.25 Gm.        | 1.65 Gm.               |
| PHOSPHORUS . . . . .             | 0.25 Gm.        | 0.903 Gm.              |
| IRON . . . . .                   | 10.5 mg.        | 11.9 mg.               |
| COPPER . . . . .                 | 0.5 mg.         | 0.5 mg.                |
| VITAMIN A . . . . .              | 1500 U.S.P.U.   | 2953 U.S.P.U.          |
| VITAMIN D . . . . .              | 435 U.S.P.U.    | 432 U.S.P.U.           |
| VITAMIN B <sub>1</sub> . . . . . | 170 U.S.P.U.    | 302 U.S.P.U.           |
| RIBOFLAVIN . . . . .             | 0.25 mg.        | 1.28 mg.               |

\*Each serving made with 8 oz. milk; based on average reported values for milk.

NEW IMPROVED



# Ovaltine

2 KINDS—PLAIN AND CHOCOLATE FLAVORED

Ovaltine now comes in 2 forms—plain, and sweet chocolate flavored. Serving for serving, they are virtually identical in nutritional value.

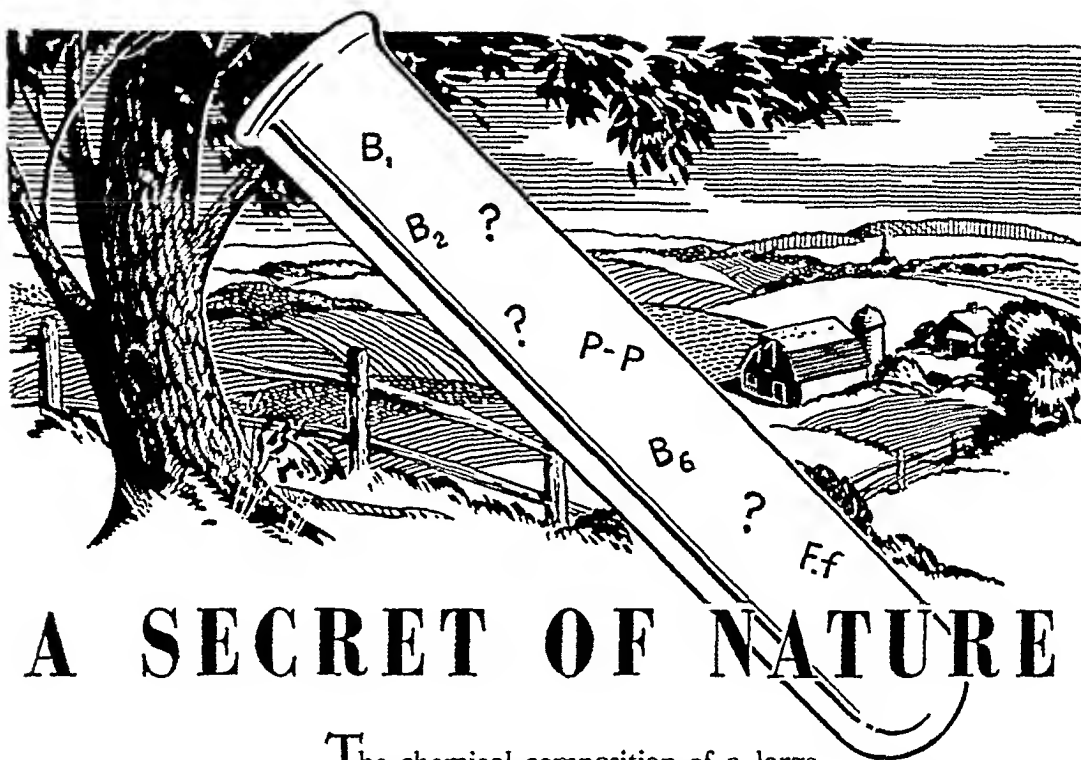
Physicians are invited to send for a supply of individual servings of New Improved Ovaltine. The Wander Company, 360 North Michigan Avenue, Chicago, Illinois

# *The American Journal of* DIGESTIVE DISEASES

*The Official Publication of*  
THE AMERICAN GASTRO-ENTEROLOGICAL ASSOCIATION

## CONTRIBUTIONS

|   | Page |
|---|------|
| INDETERMINATE FEVER CAUSED BY PERIRECTAL ABSCESS— <i>Wilson Weisel, M.D., E. G. Wakefield, M.D. and Newton D. Smith, M.D.</i> - - - - -   | 181  |
| THE INTRAVENOUS MODIFICATION OF THE HIPPURIC ACID TEST OF LIVER FUNCTION— <i>R. H. Moser, M.D., B. D. Rosenak, M.D. and R. J. Hasterlik, M.D.</i> - - - - -   | 183  |
| ETIOLOGY OF ACUTE PANCREATITIS— <i>H. L. Popper, M.D.</i> - - - - -   | 186  |
| FEAR AND GASTRIC ACIDITY— <i>Frederick Holzcl</i> - - - - -   | 188  |
| A VITAMIN SURVEY OF NORMAL INDUSTRIAL WORKMEN— <i>J. G. Schnedorf, M.D., Ph.D., C. J. Weber, M.D., Ph.D. and Logan Clendening, M.D.</i> - - - - -   | 188  |
| SUPERFICIAL ULCERATIVE GASTRITIS FOLLOWING TRIPARSAMIDE THERAPY FOR SYPHILIS— <i>I. H. Einsel, M.D.</i> - - - - -   | 191  |
| GASTROJEJUNO-COLIC FISTULA— <i>Justin J. Stein, M.D., F.A.C.S.</i> - - - - -  | 192  |
| DUODENO-COLIC AND GASTROJEJUNO-COLIC FISTULA: A COMPLICATION OF CARCINOMA. REPORT OF TWO CASES— <i>Maurice Feldman, M.D.</i> - - - - -  | 195  |
| TRICHOBEZOAR. REPORT OF A CASE— <i>Jerome S. Levy, M.D. and Randolph T. Smith, M.D.</i> - - - - -   | 198  |
| CELLULOSE SPLITTING MICRO-ORGANISMS IN HUMAN FECES— <i>Nell Hirschberg, Ph.D.</i> - - - - -   | 200  |
| THE INFLUENCE OF CERTAIN COMMONLY USED DRUGS ON THE RATE OF GASTRIC EMPTYING IN THE NORMAL HUMAN SUBJECT AS DETERMINED BY AN INTUBATION TECHNIQUE. (ATROPINE, MORPHINE, BENZEDRINE, PROSTIGMINE, NITROGLYCERINE, SYNTROPAN, MECHOLYL, ERGOTAMINE TARTRATE AND SODIUM BICARBONATE)— <i>Jarrett H. Folley, M.D. and W. Osler Abbott, M.D.</i> - - - - - | 202  |
| SOME FACTORS CONCERNED IN THE PRODUCTION OF EXPERIMENTAL ULCERATION OF THE G-I TRACT IN CATS— <i>M. J. Schiffrin, Ph.D. and Althea A. Warren, M.D.</i> - - - - -  | 205  |
| EDITORIAL:—   |      |
| THE RESISTANCE OF THE GASTRIC AND INTESTINAL MUCOSA TO HYDROCHLORIC ACID AND ARTIFICIAL GASTRIC JUICE   | 209  |
| ABSTRACTS OF CURRENT LITERATURE - - - - -   | 210  |



# A SECRET OF NATURE

The chemical composition of a large part of Vitamin B Complex is still one of Nature's secret formulas.

Animal experiments clearly show this, and clinical results demonstrate the need for **WHOLE NATURAL B COMPLEX** in preference to mixtures of synthetic factors.

## BEZON

Trade Mark

### WHOLE NATURAL B COMPLEX

One capsule of BEZON a day meets the full requirement of thiamin and riboflavin, together with all the other natural B factors.

**Now Available:** BEZON in bottles of 100 as well as bottles of 30 capsules. BEZON is made only in the distinctive two-color gelatin capsule.

*Samples and literature available on request.*

**The Complete  
Vitamin Arch**

## PENDRON

Reg. U. S. Pat. Off.

Each Pendron capsule furnishes the eight known essential vitamins in amounts which are recognized by the medical profession and governmental agencies as the minimum daily requirement for optimum nutrition. Available in bottles of 30 capsules. Full month's supply.

*Products of Nutrition Research Laboratories are  
promoted only through the medical profession.*

## NUTRITION RESEARCH LABORATORIES

4210 Peterson Avenue, Chicago, Illinois



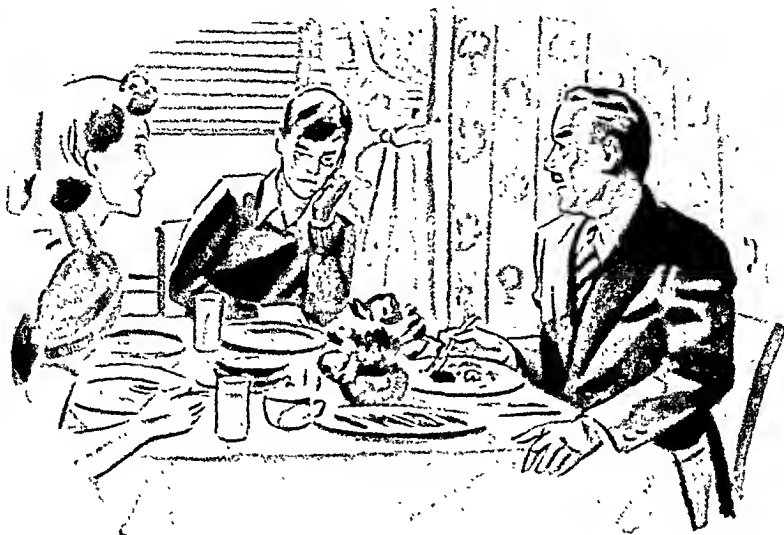
*The American Journal of*

DIGESTIVE DISEASES

The Official Publication of  
THE AMERICAN GASTRO-ENTEROLOGICAL ASSOCIATION

CONTRIBUTIONS

|  | Page |
|--|------|
| A CLINICAL ROENTGENOLOGICAL REVIEW OF THE LITERATURE FOR 1941, PERTAINING TO THE DIGESTIVE TRACT— <i>Maurice Feldman, M.D.</i> - - - - -   | 211  |
| HIDRADENITIS SUPPURATIVA: DIAGNOSIS AND TREATMENT OF ITS PERIANAL MANIFESTATIONS— <i>Raymond J. Jackman, M.D.</i>  | 220  |
| THE LIPOLYTIC ANALYSIS OF THE DUODENAL CONTENTS— <i>Bradford N. Craver, Ph.D. and Burnham S. Walker, M.D.</i> - -  | 223  |
| PURPURA DUE TO VITAMIN K DEFICIENCY IN ANOREXIA NERVOSA— <i>P. M. Aggeler, M.D., S. P. Lucia, M.D. and H. M. Fishbon, M.D.</i> - - - - -   | 227  |
| THE USE OF SULFAGUANIDINE IN NON-SPECIFIC ULCERATIVE COLITIS AND OTHER INFECTIONS OF THE BOWEL— <i>Joseph B. Kirsner, M.D., Ph.D., Enid C. Rodaniche, Ph.D. and Walter Lincoln Palmer, M.D., Ph.D.</i> - - - - - | 229  |
| EXPERIMENTS ON THE RELATIONSHIP OF THE NEUROHYPOPHYSIS TO GASTRIC SECRETION— <i>E. G. Gross, M.D., W. R. Ingram, Ph.D. and N. W. Fugo, Ph.D.</i> - - - - -   | 234  |
| STRICTURE OF THE RECTUM DUE TO LYMPHOGRANULOMA VENEREUM—SYMPTOMS AND TREATMENT WITH SODIUM SULFANILYL SULFANILATE— <i>Joseph G. Levy, M.D., Ernest C. Holder, M.D. and Jesse G. M. Bullock, M.D.</i> - - - - -   | 237  |
| EDITORIAL:—  |      |
| A REMARKABLE STUDY OF 10,890 CASES OF CANCER OF THE STOMACH. - - - - -   | 239  |
| ABSTRACTS OF CURRENT LITERATURE - - - - -  | IX   |



# *In the* **NUTRITIONAL** *demands* OF THE ADOLESCENT YEARS

The sudden acceleration of growth and development, which characterizes the adolescent period, sharply increases the metabolic requirements for most of the specific nutrients.

New Improved Ovaltine is an advantageous means of satisfying the larger nutritional needs of adolescence. It provides an appreciable percentage of the daily need of proteins, vitamins, and minerals. The palatable taste of this concentrated food drink is especially attractive to both children and adults, hence encourages consumption

of whatever quantities may be deemed necessary by the physician.

Three daily servings (1½ oz.) of New Improved Ovaltine provide:

|                                  | Dry<br>Ovaltine | Ovaltine<br>with milk* |
|----------------------------------|-----------------|------------------------|
| PROTEIN . . . . .                | 6.00 Gm.        | 31.20 Gm.              |
| CARBOHYDRATE . . . . .           | 30.00 Gm.       | 65.00 Gm.              |
| FAT . . . . .                    | 3.15 Gm.        | 31.95 Gm.              |
| CALCIUM . . . . .                | 0.25 Gm.        | 1.05 Gm.               |
| PHOSPHORUS . . . . .             | 0.25 Gm.        | 0.993 Gm.              |
| IRON . . . . .                   | 10.5 mg.        | 11.9 mg.               |
| COPPER . . . . .                 | 0.5 mg.         | 0.5 mg.                |
| VITAMIN A . . . . .              | 1500 U.S.P.U.   | 2952 U.S.P.U.          |
| VITAMIN D . . . . .              | 405 U.S.P.U.    | 432 U.S.P.U.           |
| VITAMIN B <sub>1</sub> . . . . . | 300 U.S.P.U.    | 432 U.S.P.U.           |
| RIBOFLAVIN . . . . .             | 0.25 mg.        | 1.28 mg.               |

\*Each serving made with 8 oz. milk; based on average reported values for milk.

**NEW IMPROVED**



# *Ovaltine*

**2 KINDS—PLAIN AND CHOCOLATE FLAVORED**  
Ovaltine now comes in 2 forms—plain, and sweet chocolate flavored. Serving for serving, they are virtually identical in nutritional value.

Physicians are invited to send for a supply of individual servings of New Improved Ovaltine. The Wander Company, 360 North Michigan Avenue, Chicago, Illinois.

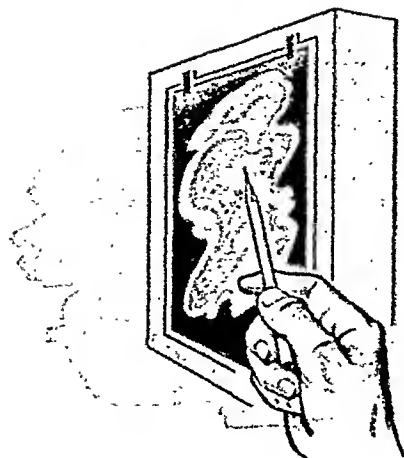
*The American Journal of*

# DIGESTIVE DISEASES

*The Official Publication of*  
THE AMERICAN GASTRO-ENTEROLOGICAL ASSOCIATION

## CONTRIBUTIONS

|   | <i>Page</i> |
|---|-------------|
| THE WAR'S CHALLENGE TO GASTRO-ENTEROLOGY. PRESIDENTIAL ADDRESS— <i>Russell S. Boles, M.D.</i> - - - - -   | 241         |
| PEPTIC ULCER AND IRRITABLE COLON IN THE ARMY— <i>Donald T. Chamberlin, M.D.</i> - - - - -   | 245         |
| DISEASES OF ANOURECTUM AND COLON. REVIEW OF CERTAIN RECENT CONTRIBUTIONS— <i>Robert Turell, M.D.</i> - - - - -  | 248         |
| GASTRIC SIMILARITIES AND DIFFERENCES BETWEEN TROPICAL SPRUE AND PERNICIOUS ANEMIA— <i>A. Rodriguez Olleros</i> - - -  | 261         |
| STUDIES IN HUMAN BILIARY PHYSIOLOGY. VI. COMPOSITION OF CONTINUOUSLY COLLECTED FRACTIONS OF LIVER BILE ON STARVATION AND AFTER HIGH CARBOHYDRATE FEEDING— <i>Mendel Jacobi, M.D., Benjamin Kogut, M.D., I. Charles Zuckerman, M.D., Lester Weil, M.A. and Bernard Klein, M.A.</i> - - - - - | 264         |
| THE INFLUENCE OF SINGLE AND MULTIPLE B COMPLEX DEFICIENCIES UPON THE MOTILITY OF THE GASTRO-INTESTINAL TRACT— <i>Gustav J. Martin, Marvin R. Thompson and Jose De Carvajal-Forcio</i> - - - - -   | 268         |
| LECTURESHIP NAMED FOR DR. JULIUS FRIEDENWALD - - - - -  | 273         |
| COMMITTEE ON MILITARY PREPAREDNESS - - - - -  | 273         |
| ABSTRACTS OF CURRENT LITERATURE - - - - -   | IX          |



In Atonic Constipation  
peristalsis can be naturally stimulated by the  
bland, non-allergy producing bulk of

# Mucilose

---



*This highly purified hemicellulose is  
available in 4 oz. and 16 oz. bottles  
as Mucilose Flakes and Mucilose  
Granules; and in 4 oz. bottles as  
Mucilose Granules with Kasagra*

Frederick Stearns & Company

---



*Since 1855 . . .* ESSENTIALS OF THE PHYSICIAN'S ARMAMENTARIUM

NEW YORK KANSAS CITY SAN FRANCISCO WINDSOR, ONTARIO DETROIT, MICH. SYDNEY, AUSTRALIA AUCKLAND, NEW ZEALAND

# *The American Journal of* DIGESTIVE DISEASES

*The Official Publication of*  
THE AMERICAN GASTRO-ENTEROLOGICAL ASSOCIATION

## CONTRIBUTIONS

|  | Page  |
|--|-------|
| GASTRIC SECRETION IN THE NEWBORN— <i>M. H. F. Friedman, Ph.D.</i> - - - - -  | 275   |
| THE ACIDITY OF THE "ULCER-BEARING AREA" OF THE DUODENUM IN NORMAL PERSONS— <i>J. Edward Berk, M.D., M.Sc. (Med.), Martin E. Rehfuess, M.D. and J. Earl Thomas, M.D.</i> - - - - -  | 276   |
| SOME OBSERVATIONS ON A PATIENT WITH AN ILEOSTOMY BEARING ON THE DIAGNOSIS OF "IRRITABLE COLON"— <i>Edward S. Emery, Jr., M.D.</i> - - - - -  | 281   |
| SEGMENTAL SPASMS OF THE ESOPHAGUS AND THEIR RELATION TO PARKINSONISM— <i>Abraham Pemner, M.D. and Leonard J. Druckerman, M.D.</i> - - - - -  | 282   |
| REDUNDANT GASTRIC MUCOSA SIMULATING CARCINOMA OF THE STOMACH— <i>Herman J. Moersch, M.D. and James F. Weir, M.D.</i> - - - - -   | 287   |
| BENIGN SUBMUCOSAL TUMORS OF THE STOMACH: A GASTROSCOPIC STUDY— <i>Rudolf Schindler, M.D., David J. Sandweiss, M.D. and I. Lew Mintz, M.D.</i> - - - - -  | 289   |
| THE MODE OF THE LAXATIVE ACTION OF PHENOLPHTHALEIN— <i>Philip Blick, Ph.D., J. B. Berardi, M.D. and Oskar Wozasek, M.D.</i> - - - - -  | 292   |
| THE EFFECT OF GASTRIC HYPERSECRETION ON THE REACTION AND NEUTRALIZING ABILITY OF THE CONTENTS OF THE FIRST PART OF THE DUODENUM IN NORMAL DOGS— <i>J. Edward Berk, M.D., M.Sc. (Med.), J. Earl Thomas, M.D. and M. E. Rehfuess, M.D.</i> - - - - - | 297   |
| IMPENDING GANGRENE OF THE FOOT FOLLOWING TREATMENT FOR PRURITUS OF JAUNDICE WITH ERGOTAMINE TARTRATE: REPORT OF CASE— <i>Lucian A. Smith, M.D. and George B. Eusterman, M.D.</i> - - - - -   | 301   |
| CONTRIBUTIONS MADE TO KNOWLEDGE IN REGARD TO THE PANCREAS IN 1941— <i>R. Elman, M.D. and A. M. Large, M.D.</i> - -   | 303   |
| A PLEA FOR EARLY DIAGNOSIS OF CANCER OF THE COLON— <i>Knox Brittain, M.D.</i> - - - - -  | 307   |
| ABSTRACTS OF CURRENT LITERATURE - - - - -  | IX    |
| BOOK REVIEWS - - - - -   | XXXII |





## MUST OLD AGE MEAN *Feebleness?*

Weakness and infirmity are usually regarded as normal concomitants of senility, yet in many instances they need not develop. Examination of the diets chosen by many older persons discloses nutritional inadequacies which might readily account for weakness and poor physical endurance. In most instances such diets, chosen because they are thought to be "easier digested," are seriously deficient in essential nutrients.

New Improved Ovaltine is a rich source of the specific nutrients most likely to be lacking in the self-chosen diets of the aged. Hence it can be expected to be of real aid in correcting many subclinical deficiencies. This delicious food drink, more easily digested than milk alone, rarely produces

epigastric distress or abdominal discomfort. The three recommended daily servings contribute significant amounts of protein, calcium, iron, and the essential vitamins.

Three daily servings (1½ oz.) of New Improved Ovaltine provide:

|                                  | Dry<br>Ovaltine | Ovaltine<br>with milk* |
|----------------------------------|-----------------|------------------------|
| PROTEIN . . . . .                | 6.00 Gm.        | 31.29 Gm.              |
| CARBOHYDRATE . . . . .           | 30.00 Gm.       | 66.00 Gm.              |
| FAT . . . . .                    | 3.15 Gm.        | 31.95 Gm.              |
| CALCIUM . . . . .                | 0.25 Gm.        | 1.05 Gm.               |
| PHOSPHORUS . . . . .             | 0.25 Gm.        | 0.923 Gm.              |
| IRON . . . . .                   | 10.5 mg.        | 11.9 mg.               |
| COPPER . . . . .                 | 0.5 mg.         | 0.5 mg.                |
| VITAMIN A . . . . .              | 1500 U.S.P.U.   | 2353 U.S.P.U.          |
| VITAMIN D . . . . .              | 435 U.S.P.U.    | 432 U.S.P.U.           |
| VITAMIN B <sub>1</sub> . . . . . | 300 U.S.P.U.    | 432 U.S.P.U.           |
| RIBOFLAVIN . . . . .             | 0.25 mg.        | 1.28 mg.               |

\*Each serving made with 4oz. milk; based on average reported values for milk.



NEW IMPROVED

# Ovaltine

2 KINDS—PLAIN AND CHOCOLATE FLAVORED

Ovaltine now comes in 2 forms—plain, and sweet chocolate flavored. Serving for serving, they are virtually identical in nutritional value.

Physicians are invited to send for a supply of individual servings of New Improved Ovaltine. The Wander Company, 360 North Michigan Avenue, Chicago, Ill.

# The American Journal of DIGESTIVE DISEASES

The Official Publication of  
THE AMERICAN GASTRO-ENTEROLOGICAL ASSOCIATION

## CONTRIBUTIONS

|   | Page     |
|---|----------|
| NUTRITIONAL PROBLEMS IN WARTIME— <i>Clifford J. Barborka, M.D.</i> - - - - -  | 309      |
| THE NONFUNCTIONING GASTRO-ENTERIC STOMA. DIAGNOSTIC STUDY OF SIXTY-TWO SURGICALLY DEMONSTRATED CASES—<br><i>George B. Eusterman, M.D., B. R. Kirklin, M.D. and Carl G. Morlock, M.D.</i> - - - - -    | 313      |
| FOLLOW-UP RESULTS IN SUB-TOTAL GASTRIC RESECTION FOR ULCER— <i>Reynold E. Church, M.D. and J. William Hinton, M.D.</i>  | 317      |
| THE OBSTRUCTED PEPTIC ULCER— <i>S. Allen Wilkinson, M.D.</i> - - - - -  | 321      |
| A SUMMARY OF PREVENTIVE METHODS IN CERTAIN TROPICAL DISEASES— <i>Z. Bercovitz, M.D.</i> - - - - -   | 327      |
| METABOLIC DISTURBANCES IN WORKERS EXPOSED TO DINITROTOLUENE— <i>Lemuel C. McGee, M.D., Ph.D., Alexander McCausland, M.D., C. A. Plume, M.D. and N. C. Marlett, M.D.</i> - - - - -                     | 329      |
| THE EFFICACY OF THE DRIP METHOD IN THE REDUCTION OF GASTRIC ACIDITY— <i>Albert Cornell, M.D., Franklin Hollander, Ph.D. and Asher Winkelstein, M.D.</i> - - - - -                                     | 332      |
| CHRONIC GASTRIC ULCER IN A SIX YEAR OLD CHILD— <i>Manfred Kraemer, M.D.</i> - - - - -   | 338      |
| ANACIDITY AND GASTRITIS ASSOCIATED WITH GASTRIC CARCINOMA— <i>Rudolf Schindler, M.D. and William M. Smith, M.D.</i>   | 340      |
| DIAGNOSTIC VALUE OF SERUM CHOLINESTERASE DETERMINATIONS IN JAUNDICE AND IN CIRRHOSIS OF THE LIVER— <i>Arthur Schifrin, M.D., Lester Tuchman, M.D. and William Antopol, M.D.</i> - - - - -             | 342      |
| A CONSIDERATION OF THE HEPATICO-RENAL SYNDROME— <i>Chas. Gordon Heyd, B.A., M.D., F.A.C.S., D.M.Sc.</i> - - - - -   | 348      |
| II. INTESTINAL ABSORPTION OF AN AMINO-ACID MIXTURE IN PATIENTS WITH CHRONIC IDIOPATHIC ULCERATIVE COLITIS AND ENTERO-COLITIS— <i>I. Zetzel, M.D., B. M. Banks, M.D. and E. Sagall, M.D.</i> - - - - - | 350      |
| THE EFFECT OF HISTAMINE ON CINCHOPHEN ULCERS PRODUCED IN DOGS— <i>B. Slutzky, M.D. and N. Dietz, Ph.D.</i> - - - - -  | 352      |
| CLINICAL STUDIES OF AMINO ACIDS. I. THE EFFECT OF ORAL ADMINISTRATION OF A SOLUTION OF AN AMINO ACIDS MIXTURE ON GASTRIC ACIDITY— <i>Jerome S. Levy, M.D. and Kenneth A. Siler, Ph.D.</i> - - - - -   | 354      |
| THE USE OF SULFAGUANIDINE FOR ULCERATIVE COLITIS— <i>Manfred Kraemer, M.D.</i> - - - - -  | 356      |
| EDITORIALS:—  |          |
| HOW VITAMINS AFFECT THE BODY'S METABOLISM - - - - -   | 357      |
| THE NEUROGENIC PRODUCTION OF DUODENAL ULCER— <i>Burrill B. Crohn</i> - - - - -  | 358      |
| ABSTRACTS OF CURRENT LITERATURE - - - - -   | 358      |
| BOOK REVIEWS - - - - -  | -XXXVIII |

# Young Stomachs— and Old

Would it not be a reasonable analogy to say that the digestive organs of a newborn infant and those of an adult afflicted with a digestive disorder are in a sense quite similar?

Both require foods that are bland and easily digested, for, of course, foods other than these may easily have irritating effects resulting in serious digestive disturbance.

Does it not therefore follow, and very logically, that Pet Milk, which by extensive use has proved to be extraordinarily suitable for the feeding of infants, even those prematurely born, should be equally well adapted for use in the dietary employed in the treatment of adult digestive disorders?

And would it not be sound therapy, when prescribing for the disordered digestive system, to specify Irradiated Pet Milk—a safe readily digestible milk, containing an extra supply of vitamin D—and available at a lower price generally than ordinary milk.

*We will gladly send literature and samples on request.*

PET MILK COMPANY, 1446j Arcade Building St. Louis, Missouri

*Please send me,  
free of charge,*

- ☐ Samples of Irradiated Pet Milk
- ☐ Reprint of report on "The Use of Evaporated Milk in Digestive Disorders, Particularly Peptic Ulcers"
- ☐ Copies of "Victory Lunch Box Meals"

Dr. \_\_\_\_\_ Address \_\_\_\_\_

City \_\_\_\_\_ State \_\_\_\_\_

\*Attach prescription form or letterhead to coupon. Offer limited to physicians of Continental U.S.A.



# The American Journal of DIGESTIVE DISEASES

The Official Publication of  
THE AMERICAN GASTRO-ENTEROLOGICAL ASSOCIATION

## CONTRIBUTIONS

|   | <i>Page</i> |
|---|-------------|
| THE TREATMENT OF INTESTINAL DISORDERS IN THE MILITARY FORCES— <i>L. C. Gatewood</i> - - - - -   | 359         |
| RELATIONSHIP OF THE HYPOTHALAMUS TO THE LARGE BOWEL— <i>Donal Sheehan, M.D.</i> - - - - -   | 361         |
| CONCERNING THE INFLUENCE OF GLUCOSE ON THE RESPONSE OF THE HUMAN STOMACH TO TEST MEALS— <i>Harry Shay, M.D., J. Gershon-Cohen, M.D., D.Sc. (Med.), Samuel S. Fels, LL.D. and Herman Sipler, A.B.</i> - - - - -      | 363         |
| THE RELATIONSHIP BETWEEN GASTRIC ACIDITY AND CALCIUM— <i>Frank C. Val Dez, M.D. and Julius Sendroy, Jr., Ph.D.</i> - - - - -  | 367         |
| THE ACID FACTOR IN DUODENAL ULCER AS EVALUATED BY THE ACIDITY AND NEUTRALIZING ABILITY IN THE DUODENAL BULB— <i>J. Edward Berk, M.D., M.Sc. (Med.), J. Earl Thomas, M.D. and Martin E. Rehfuess, M.D.</i> - - - - - | 371         |
| THE RELATIONSHIP BETWEEN GASTRO-DUODENAL MOTILITY PHASES AND SYMPTOMS ASSOCIATED WITH DUODENAL ULCER IN THE HUMAN— <i>Thomas L. Patterson, Ph.D. and David J. Sandweiss, M.D.</i> - - - - -                         | 375         |
| CONGENITAL ANOMALIES OF THE PRIMARY MIDGUT LOOP— <i>Joseph M. Miller, M.D. and E. G. Wakefield, M.D.</i> - - - - -  | 383         |
| EFFECT OF HEMICELLULOSE HYDROGELS ON THE CHARACTER OF THE STOOL AND BOWEL MOVEMENT— <i>Richard Bauer, M.D.</i> - - - - -  | 387         |
| THE GASTRO-INTESTINAL SECTION—ARMY GENERAL HOSPITAL— <i>Augustus A. Hall, M.D.</i> - - - - -  | 389         |
| INFRA-RED PHOTOGRAPHY OF THE ABDOMINAL WALL— <i>Edgar Wayburn, M.D.</i> - - - - -   | 392         |
| THE AMOUNT OF FAT IN THE BLOOD AFTER A MEAL AS ESTIMATED BY COUNTING THE CHYLOMICRONS— <i>Ralph R. Cooper, M.D. and Harry Lusk, M.D.</i> - - - - -  | 395         |
| COMPLETE BILIARY OBSTRUCTION COMPLICATING DUODENAL ULCER; PERFORATION OF THE ULCER FOLLOWED BY IMMEDIATE RELEASE OF THE OBSTRUCTION— <i>Samuel Levine, M.D. and George B. Gordon, M.D.</i> - - - - -                | 397         |
| ABSTRACTS OF CURRENT LITERATURE - - - - -   | 398         |
| BOOK REVIEWS - - - - -  | XXX         |



## Specialized G-I Diets

### NEED NOT BE UNBALANCED

The problem of supplying adequate amounts of essential nutrients, when the diet must be bland and low in residue, loses its difficulty when New Improved Ovaltine is used as the mealtime beverage and for supplemental feedings.

This delicious food drink provides a high percentage of the daily requirements of biologically adequate protein, essential minerals and vitamins, in a form not only palatable but also readily utilized by the organism, with a minimum of digestive effort.

Since specialized G-I diets are usually high in carbohydrates, it is of moment

also that Ovaltine aids in starch digestion through the action of its high diastatic malt content.

Three daily servings (1 1/2 oz.) of New Improved Ovaltine provide:

|                        | Dry Ovaltine  | Ovaltine with milk* |
|------------------------|---------------|---------------------|
| PROTEIN . . . . .      | 6.00 Gm.      | 31.20 Gm.           |
| CARBOHYDRATE . . . . . | 29.00 Gm.     | 66.00 Gm.           |
| FAT . . . . .          | 3.15 Gm.      | 31.55 Gm.           |
| CALCIUM . . . . .      | 0.25 Gm.      | 1.05 Gm.            |
| PHOSPHORUS . . . . .   | 0.25 Gm.      | 0.93 Gm.            |
| IRON . . . . .         | 10.5 mg.      | 11.9 mg.            |
| COPPER . . . . .       | 0.5 mg.       | 0.5 mg.             |
| VITAMIN A . . . . .    | 1570 U.S.P.U. | 2953 U.S.P.U.       |
| VITAMIN D . . . . .    | 4.5 U.S.P.U.  | 432 U.S.P.U.        |
| VITAMIN E . . . . .    | 350 U.S.P.U.  | 432 U.S.P.U.        |
| BIOTIN . . . . .       | 0.25 mg.      | 1.23 mg.            |

\*Each serving made with 8 oz. milk, based on average reported values for milk.



NEW IMPROVED

# Ovaltine

2 KINDS—PLAIN AND CHOCOLATE FLAVORED

Ovaltine now comes in 2 forms—plain, and sweet chocolate flavored. Serving for serving, they are virtually identical in nutritional value.

Physicians are invited to send for a supply of individual servings of New Improved Ovaltine. The Wander Company, 360 North Michigan Avenue, Chicago, Illinois.

# *The American Journal of* DIGESTIVE DISEASES

*An Independent Publication*  
DEVOTED TO GASTRO-ENTEROLOGY AND NUTRITION

## CONTRIBUTIONS

Page

|   |         |
|---|---------|
| VARICES OF THE GALL BLADDER; ASSOCIATED WITH A MUCOSAL CYST. REPORT OF A CASE— <i>Maurice Feldman, M.D., Jerome E. Goodman, M.D. and Tobias Weinberg, M.D.</i> - - - - -                      | 399     |
| A CRITICAL ANALYSIS OF 938 GASTROSCOPIC EXAMINATIONS— <i>John F. Renshaw, M.D., George E. Clark, Jr., M.D. and John R. Forsyth, Lt., U.S.A.M.C.</i> - - - - -                                 | 401     |
| GASTRIC ATROPHY IN FAR ADVANCED PULMONARY TUBERCULOSIS COMPLICATED BY INTESTINAL TUBERCULOSIS— <i>Leo L. Hardt, M.D., F.A.C.P., Morris Weissman, M.D. and John S. Coulter, M.D.</i> - - - - - | 404     |
| GASTRIC MUCOSAL CHANGES OF TUBERCULOSIS — <i>Donovan C. Browne, M.D., Gordon McHardy, M.D. and Carl Wilcn, M.D.</i> - - - - -   | 407     |
| HISTOPATHOLOGY OF CHRONIC GASTRITIS— <i>Rudolf Schindler, M.D. and Marie Ortmayer, M.D.</i> - - - - -   | 411     |
| THE SECRETION OF WATER AS A COMPONENT OF GASTRIC ACID SECRETION— <i>Horace W. Davenport, Ph.D.</i> - - - - -  | 416     |
| PAROTID DUCT OBSTRUCTION WITHOUT CALCULUS. A SUGGESTION FOR TREATMENT— <i>Louis Pelner, M.D.</i> - - - - -  | 417     |
| PROTHROMBIN AND FIBRINOGEN STUDIES IN CHRONIC ULCERATIVE COLITIS— <i>Robert C. Page, M.D. and Z. Bercovitz, M.D.</i> - - - - -  | 419     |
| STUDIES ON COLON IRRITATION. III. BULK OF FECES— <i>Oskar Wozasek, M.D. and F. Steigmann, M.S., M.D.</i> - - - - -  | 423     |
| SERUM DIASTASE DETERMINATIONS DURING ARTIFICIALLY PRODUCED INTRA-DUODENAL PRESSURE AGAINST THE HEAD OF THE PANCREAS. PRELIMINARY REPORT— <i>S. G. Castigliano, M.D.</i> - - - - -             | 425     |
| PANCREATITIS IN ACUTE AND CHRONIC ALCOHOLISM— <i>Eugene Clark, M.D.</i> - - - - -   | 428     |
| EDITORIALS:—  |         |
| AVE ATQUE VALE - - - - -  | 431     |
| PSYCHOSOMATIC INTERRELATIONSHIPS - - - - -  | 432     |
| WILLIAM C. MENNINGER, M.D. - - - - -  | 433     |
| THE PHYSICIAN'S ATTITUDE TOWARD VITAMINS - - - - -  | 433     |
| ABSTRACTS OF CURRENT LITERATURE - - - - -   | 434     |
| BOOK REVIEWS:—  |         |
| OCCUPATIONAL TUMORS AND ALLIED DISEASES— <i>W. C. Hueper</i> - - - - -  | XXXVI   |
| SURGICAL PHYSIOLOGY— <i>Joseph Nash</i> - - - - -   | XXXVIII |
| INTESTINAL OBSTRUCTION— <i>Owen H. Wangensteen</i> - - - - -  | XXXVIII |
| ANALES DEL DISPENSARIO PUBLICO NACIONAL PARA ENFERMEDADES DEL APARATO DIGESTIVO— <i>A. Guidi Buffarini</i> - - - - -  | XXXVIII |

(INDEX NUMBER)

# VITAMIN B<sub>1</sub> DEFICIENCY

WHILE the typical case of beriberi presents a relatively simple diagnostic problem, the wide variability of the signs and symptoms of the much more frequent mild cases of vitamin B<sub>1</sub> deficiency often leads to considerable difficulty in diagnosis.

In considering the diagnosis it may be helpful to recall, as pointed out by Williams and Spies,\* that vitamin B<sub>1</sub> deficiency occurs especially among the following groups:

*The indigent, and those with improper dietary habits and idiosyncrasms.* Poorly balanced diets may be chosen inadvertently or because of financial restrictions. In addition, food fads and reducing diets may be responsible for the development of vitamin B<sub>1</sub> deficiency.

*Patients who have an organic disease.* In such patients, there may be loss of appetite or restriction of the dietary associated with the disease. In the presence of gastro-intestinal disturbances, the absorption of the vitamin may be impaired.

*Persons with increased vitamin B<sub>1</sub> requirements.* The requirement for vitamin B<sub>1</sub> is increased as a result of greatly augmented metabolism in febrile conditions, hyperthyroidism, or vigorous muscular exertion, and during pregnancy and lactation.

In cases of vitamin B<sub>1</sub> deficiency, the daily administration of adequate amounts of thiamine hydrochloride will ensure a prompt therapeutic response. When absorption from the gastro-intestinal tract is impaired, parenteral administration of thiamine hydrochloride is indicated.

## Literature on Request

\*Williams, E. K., and Spies, T. D., *Vitamin B<sub>1</sub> Deficiency in Medicine*, The Macmillan Co., New York, 1938.

**THIAMINE  
HYDROCHLORIDE  
MERCK**

Vitamin B<sub>1</sub>  
Hydrochloride



MERCK & CO. Inc. • Manufacturing Chemists RAHWAY, N. J.



# A Clinical and Laboratory Study of Plasma Lipids in Obstructive Jaundice and Several Types of Hepatic Disease\*

By

CHARLES A. JONES, M.D., D.Sc. (Med.)<sup>††</sup>

CHANGES in concentration of the lipid substances present in blood, serum, or plasma which result from various types of hepatic and biliary tract disease have been extensively studied. Most observers have found that simple obstruction of the bile ducts usually produces a hypercholesterolemia (1, 2, 3, 4, 22, 25, 26, 28, 34, 38, 43, 51, 52, 70, 80, 81, 86, 87, 90, 91). This hypercholesterolemia is usually accompanied by an increase in concentration of the other blood lipids (2, 4, 28, 29, 43, 86, 90, 91). Experimental studies in animals indicate that these same changes occur after ligation of the common bile duct (23, 26, 39, 52, 80, 87). This usual finding, however, may be modified by a number of complications. The increase in concentration of the lipids in blood may be prevented from occurring, or, if already present, decreased by concomitant liver damage whether caused by chronicity of the obstruction (1, 25, 26, 87); intercurrent infection (1, 25, 26, 67); or hepatic toxins (26, 39, 52). Poor fat absorption resulting from absence of bile in the intestine in obstructive jaundice has been thought to explain absence of increased concentration of lipids by some observers (34, 78, 79).

In contrast to the effect of biliary duct obstruction, primary disease of the liver usually results in a diminished concentration of cholesterol in blood (1, 15, 25, 26, 27, 29, 40, 43, 52, 72, 81, 83, 86, 90, 91) and the other lipids behave in a similar manner (15, 27, 29, 43, 86, 90). Feigel (27) noted that ester cholesterol was diminished in concentration along with the other serum lipids in patients with acute yellow atrophy of the liver. It remained, however, for Thannhauser and Schaber (83) to correlate this reduction in concentration of ester cholesterol with impaired hepatic function. They demonstrated that the decrease in ester cholesterol paralleled the degree of hepatic damage, a finding that has been confirmed many times (1, 25, 26, 40, 43, 51, 52, 72, 81, 90). Boyd (15) has shown that the cholesterol "estersturz" of Thannhauser and Schaber is in reality a part of a general lipopenia.

The occurrence of hypercholesterolemia in patients with obstructive jaundice seems to be well established, but concerning whether this increase in cholesterol concentration results from an increase in the free or esterified cholesterol or both has led to a considerable difference of opinion. Adler and Lemmel (1), Epstein (25), Epstein and Greenspan (26), Feigel (28) and Wendt (87) find that the increase is the result of increments in both the free and ester cholesterol

fractions. Epstein and Greenspan (26) find this hypercholesterolemia resulting from an increase in both the cholesterol esters and free cholesterol to be of such regular occurrence in obstructive jaundice that it assumes diagnostic significance if it can be correlated with an increased concentration of serum bilirubin. The hypercholesterolemia in obstructive jaundice has been found to result from an increase in the free cholesterol without a concomitant rise in the ester cholesterol by Boyd (14), Chanutin and Ludewig (23), Gardner and Gainsborough (34), Hawkins and Wright (39), Lehnher (43) and Mancke (51).

Gardner and Gainsborough (34) suggest poor fat absorption as the factor which limits the concentration of ester cholesterol in the blood of patients with obstructive jaundice. Hawkins and Wright (39) could not substantiate this finding in dogs and found that decreased cholesterol esters occurred only after the liver had been injured. Chanutin and Ludewig (23) have conclusively shown, however, that in the rat, at least, the increased plasma cholesterol concentration in the presence of bile duct obstruction (ligation of the common bile duct) is due to the increased concentration of free cholesterol without a similar increase in the cholesterol esters.

In our own experience the study of cholesterol and its esters in the blood and plasma has corresponded with that of others (65, 57) (82 Snell's discussion) in that we had not obtained the useful results expected. A study of the problem (41) has shown several factors which are operative in the production of this lack of agreement with those who find the study of cholesterol and its esters and the other lipids a useful diagnostic and prognostic procedure.

A consideration of some of these factors at this point may perhaps clarify some of this confusion. Many workers have sought to compare the results of analyses of extracts of whole blood, serum and plasma. Such results, strictly speaking, are not comparable. It has been known for a long time that cholesterol is unequally distributed between the red blood cells and the plasma or serum (38, 17) and that the cholesterol present in the erythrocytes exists only as free cholesterol. This inequality of distribution of cholesterol between the cellular and fluid elements of the blood and the absence of cholesterol esters in the cells introduces an uncontrollable variable into the determination of this substance and renders impossible strict comparison of results of whole blood analyses with those of plasma or serum. Furthermore, the well known fact that oxalated plasma usually yields results lower than serum or heparinized plasma (16, 46, 77) renders strict comparison of serum and plasma questionable.

A second and most important reason for variations in results, obtained by different workers is that the data reported have been based on analyses made with

\*From the Medical and Gastro-Enterological Services of the Graduate Hospital of the University of Pennsylvania.

††This paper represents a summary of a part of a thesis submitted to the Graduate School of Medicine of the University of Pennsylvania, in partial fulfillment of the requirements for the degree of Doctor of Medical Science, for Graduate Work in Internal Medicine.

This work was supported by the Julia M. Keim Fund.  
Read at the Annual Meeting of the American Gastro-Enterological Association at Atlantic City, N. J., May 5, 1941.



methods which vary widely in preciseness. This applies especially to methods employed for the determination of cholesterol. Pertinent is the fact that colorimetric methods used to assay cholesterol in unsaponified extracts of blood, serum or plasma yield higher results than do the methods which isolate cholesterol before and after saponification as the digitonide, and regardless of the method subsequently employed for assay. This fact, long known (31, 44, 45, 49, 53, 54, 55, 58, 69, 88) has been shown by Gardner and Williams (35), Reinhold (69), Yasuda (92), and Kelsey (42), to result from a color enhancement effect on the Lieberman-Burchard reaction of the cholesterol esters. This enhancement effect is lost if the extract is first saponified (69). This enhancement effect produces yields of cholesterol from 20 to 30 per cent higher than the true concentration. Moreover, the variability of colorimetric methods even in skilled hands at times yields astounding errors. (See Muhlbock and Kaufmann (55), Gardner and Fox (31), Man and Peters (49)). Because of this variability of methods many reports are rendered practically useless because of poor control and by the failure of many authors to estimate the trend and magnitude of the errors inherent in the methods which they have employed.

The fact that any given value for the concentration of a substance is to be interpreted as increased or decreased by disease is predicated upon a normal range of values for that substance. A wide range of normal values renders this interpretation difficult. Such is the condition that obtains with regard to the concentration of cholesterol in the blood, serum or plasma of normal individuals. Oser and Karr (61) some time ago, and Sperry (75) more recently have pointed out that wider differences in the normal range of cholesterol concentration exist than is usually conceded. Conversely, Sperry (75) has shown that the ratio of free to total cholesterol varies within very narrow limits in health. The magnitude of these ranges will be discussed later, but it is germane at this point to indicate that the wide range of variation in cholesterol concentration in normal individuals, and the narrow limits of variation of the ratio of free to total cholesterol have contributed to the production of conflicting results.

Other factors which may contribute to the somewhat discordant results of various workers are derived from the fact that certain physiologic and pathologic factors contribute in a non-specific manner to the specific disease effect. Of these factors, age (63), sex (6, 32), race (65), obesity and normal variations in diet (5, 48) and exercise (11, 67, 68) produce little detectable effect. The effect of menstruation is usually thought to produce a decrease in concentration of cholesterol (59, 60, 56) but this is disputed by Man and Gildea (48). Body build in that the pycnic male is more apt to have serum lipid concentrations in the upper limits of normal has been found by Gildea, Kohn and Man. Lability of the vasomotor apparatus (50) and vegetative and emotional disorders indicative of basal ganglia dysfunction tend to produce increase in concentration of the serum lipids (37).

Starvation at first produced a lipemia, of more regular occurrence in the obese than in the thin individual (6), but prolongation of the starvation period

induces a lipopenia associated with hypoproteinemia (47). The effect of abnormal diets is equivocal. Most workers agree that ingestion of single meal produces little changes in lipid concentration in the post absorptive state, although some workers indicate that prolonged ingestion of diets with a high fat content tends to cause an increased concentration of lipids in the blood.

Man and Gildea (48) report wide variations in the concentration of various serum lipids from time to time in individuals who have been studied for varying periods of time up to 4 years. Yet despite this wide variation of total values the variation about the mean value in this report is but slightly greater than the variations in serum cholesterol found by Turner and Steiner (85) and Sperry (76) who conclude that an individual has a mean value for total cholesterol from which large variations do not occur, and that this can be traced from month to month and year to year. Boyd (11) found little diurnal variation in the plasma lipids in young women despite exercise, meals, sleep, etc.

Among the pathologic factors which may add to the specific effect of disease, fever which produces a lipopenic effect (25), infection of any sort which causes a reduction in the ratio of free to total cholesterol (75, 82), and anemia which causes an increase in neutral fat and a decrease in phospholipid and cholesterol (65) must be mentioned. These factors as well as pathologic malnutrition are the counter parts of a host of diseases and in most cases must be active in producing some of the changes observed. Inhalation anesthetics at first produce a lipopenia (first 8 hours) and a subsequent lipemia characterized by an increase in free cholesterol (6, 12).

While the effect of many of the technical, physiological and pathological factors which may non-specifically contribute to the effect of specific disease on the concentration of the plasma lipids is known, few of the reports contain sufficient data to permit adequate evaluation of these factors. Moreover, few of the reports offer any data concerning the status of the liver with respect to its effect on the plasma lipids other than cholesterol and its esters. That study was undertaken with the idea of controlling as many of those factors as possible, and to correlate from clinical, laboratory, operative and pathological data the changes observed in the concentration of the various plasma lipids. In the interpretation of results where non-specific factors are uncontrollable, the possibility of their contribution to the effect observed can, at least, be noted.

#### STUDY OF THE CONCENTRATION OF PLASMA LIPIDS IN NORMAL SUBJECTS

Extracts of heparinized plasma obtained from twenty-six normal individuals were prepared by Boyd's (13) method of cold dilution, and assayed by Boyd's (14) adaptations of Bloor's (7; 8) micro oxidative procedures after slight modification (41). In our hands this method has proven quite satisfactory. With stock solutions of fatty material the average difference between duplicate determinations of fatty acids was only 3.5 per cent, although an occasional difference as great as 9 per cent was noted. With phospholipids the average difference was only 2.8 per cent with an occasional difference as great as 6 per cent. The average difference in cholesterol determi-

SUMMARY TABLE I  
*Lipids\**

|                    | Total Lipid | Neutral Fat | Total Fatty Acids | Phospho-Lipids | Total   | Cholesterol Ester | Free  | Per Cent Free in Total Cholesterol |
|--------------------|-------------|-------------|-------------------|----------------|---------|-------------------|-------|------------------------------------|
| Range              | 1016-474    | 358-40      | 633-274           | 321-120        | 284-145 | 195-103           | 89-42 | 26.5%-32.8%                        |
| Mean               | 616         | 135         | 353               | 203            | 189     | 132               | 57    | 30.0%                              |
| S. D.              | ± 114       | ± 59        | ± 77.3            | ± 35.7         | ± 29.4  | ± 21              | ± 10  | ± 1.96                             |
| Per cent deviation | 18.5        | 44          | 21.9              | 17.5           | 15.5    | 15.9              | 17.5  | 6.5                                |

*Plasma proteins\*\**

|                    | Total     | Albumin   | Globulin  | Fibrinogen |
|--------------------|-----------|-----------|-----------|------------|
| Range              | 7.88-6.41 | 5.58-4.18 | 2.74-1.86 | 0.61-0.32  |
| Mean               | 7.19      | 4.91      | 2.28      | 0.44       |
| S. D.              | ± 0.34    | ± 0.39    | ± 0.26    | ± 0.084    |
| Per cent deviation | 4.7       | 7.9       | 11.4      | 19.0       |

\*Values expressed in milligrams per 100 cc. plasma.

\*\*Values expressed in grams per 100 cc. plasma.

nations was only 1.6 per cent and in no instance was there a difference greater than 3 per cent. All digitonin used was tested against known amounts of cholesterol added to fatty solutions. Under these conditions recovery of cholesterol averaged 97 per cent which is in good agreement with Boyd's (9) finding. Despite the occurrence of several rather large errors with individual lipids, total lipids calculated from the same results never varied by more than 3.4 per cent and the average difference was only 1.4 per cent. This represents one of the advantages of the use of such a method where all lipid substances are determined or calculated from data obtained by use of the same technical procedure. Errors tend to cancel one another and one value serves as a check on the other.

Blood was collected with minimal stasis in the morning during fasting, heparinized, centrifugalized and extracts prepared and stored in glassware fitted with all glass joints. No preliminary dietary regulation was attempted, but no unusual condition was present which presumably might have altered the concentration of plasma lipids.

Plasma proteins were determined on the same sample of plasma by the method of Campbell and Hanna (19, 20, 21) to serve as a check against gross

nutritional changes and hemoconcentration whether mechanically or physiologically produced.

A statistical summary of the results of these studies is presented in Table I.

For convenience in comparison of these results with those of others, Tables II and III have been compared. The differences are clearly demonstrated. Since cholesterol is the lipid substance most frequently studied, it requires more attention. Table IV has been compiled for convenience of comparison of the results of these studies with those of others. The values of cholesterol presented represent the maximum and minimum values taken from the various authors. The extremes of all these values of total cholesterol concentration in serum and plasma (109-404 milligrams per 100 cc.) demonstrate the wide range of values for this lipid in normal individuals and clearly shows how difficult is the interpretation of any given value as increased or decreased in the absence of an adequate normal control series of values regardless of what method is used.

Table V was compiled to indicate the relationship of free to total cholesterol. By inspection it may be seen that despite the wide variation in the concentration of serum or plasma cholesterol the percentage of free in total cholesterol is approximately 30 per

TABLE II

|  | Maximum           | Minimum |
|--|-------------------|---------|
| Total lipids                             | 820               | 570     |
| Neutral fat                              | 200               | 0       |
| Fatty acids                              | 420               | 190     |
| Lipoid phosphorus calculated as lecithin | 330               | 175     |
| Cholesterol, total                       | 230               | 100     |
| Cholesterol, free                        | 30 to 60 per cent |         |
| Cholesterol, esters                      | 40 to 70 per cent |         |

Values are expressed in terms of Milligrams per 100 cc. of plasma.

From Peters and Van Slyke (65).

TABLE III

| Author   | Cholesterol |            | Pl.         | T.F.A.      | N.F.         | T.L.         |
|--|-------------|------------|-------------|-------------|--------------|--------------|
|  | Total       | Free       |             |             |              |              |
| Man and Peters* (1933)                           | 207<br>± 29 | —          | 222<br>± 29 | —           | 6            | 659<br>± 80  |
| Page, Kirk, Lewis, Thompson and Van Slyke (1935) | 232<br>± 62 | 82<br>± 17 | 181<br>± 71 |             | 225<br>± 137 | 732<br>± 216 |
| Boyd (15) (1933)                                 | 181<br>± 22 | 53<br>± 10 | 195<br>± 37 | 362<br>± 62 | 154<br>± 77  | 617<br>± 75  |
| Present Series                                   | 189<br>± 21 | 57<br>± 10 | 203<br>± 36 | 353<br>± 77 | 135<br>± 59  | 616<br>± 114 |

\*Estimates made by Page, Kirk, Lewis, Thompson and Van Slyke (109). Values in milligrams per 100 cc. plasma.

cent and the variation during health is within very narrow limits. The more variable results of Page, Kirk, Lewis, Tompson and Van Slyke (63) are probably explainable on the basis of an error in the method used by them as noted by Folch, Schneider and Van Slyke (30).

#### STUDY OF THE PLASMA LIPIDS CONCENTRATION IN SEVERAL TYPES OF HEPATIC DISEASE

The twenty-seven patients upon whom these studies were made presented a variety of forms of hepatic

TABLE IV

*Total cholesterol concentration in normals*

| Author  | Maximum | Minimum |
|---|---------|---------|
| Sperry (75)                                   | 392     | 132     |
| Page, Kirk, Lewis, Tompson and Van Slyke (63) | 376     | 109     |
| Man and Peters (49)                           | 256     | 162     |
| Pinkhardt, Bernhard and Kohn (66)             | 404     | 141     |
| Muhlbock and Kaufmann (56)                    | 322     | 147     |
| Jones   | 284     | 145     |

Values in milligrams per 100 cc.

disease: Cirrhosis of the liver (toxic and Laennec's) (14 patients); metastatic or primary carcinoma of the liver (5 patients); hemolytic jaundice due to sulfanilamide (1 patient); toxic hepatitis due to neoarsphenamine (2 patients); atypical pigmentation of the skin associated with liver damage (2 patients); and catarrhal jaundice (2 patients). Plasma lipid and plasma protein estimations were made in the same manner as in the normal subjects but were carried out as frequently as opportunity permitted.

In addition during the study, various liver function tests were executed. These included biliary drainage, cholecystographic study, galactose tolerance, glucose tolerance, urobilinogen determination in urine (Wallace and Diamond), bromsulphthalein excretion (2 mg. dose of dye), hippuric acid synthesis serum phosphatase, serum bilirubin, and, at times, serum lipase determinations.

The limitations of clinical studies based on liver function tests are well known. Usually in the presence of minimal damage and occasionally in the presence of extensive damage, none of the tests may be positive. However, many of these patients were explored surgically and a more exact idea of the condition of the liver was obtained in this manner.

Plasma protein determinations were made to detect undue rapid changes in hemoconcentration and to furnish some idea of the nutritional changes in the various subjects. It is doubtful whether protein starvation with consequent production of hypoproteinemia has any effect per se on the concentration of the plasma lipids as indicated by the animal experiments of Page, Farr and Weech (62).

A summary of the results of the lipid and protein determinations from this group of patients has been made and is presented in Table VI. Comparison of the statistical summaries of the plasma lipid concen-

tration of the normal subjects and the patients with hepatic disease shows that no statistically significant difference exists. Similar comparison of the results of the protein determinations reveals a significant decrease in plasma albumin concentration. It is interesting to note that the plasma fibrinogen concentration tends to be increased, although the increase is not great enough to be significant. The concentrations of plasma lipid are more variable in the abnormal group. Neutral fat varies most widely. This is true, also, when applied to the normal group. Neutral fat is a value calculated from residual fatty acids and hence suffers from a summation of errors in the determinations, a fact which possibly accounts for the greater variability found in this lipid. As a generalization, the wide variation of values for concentrations of the plasma lipids in both groups renders impossible the attachment of diagnostic significance to the results.

Applied to individual patients comparison of the plasma lipid concentrations of the two groups indicates that at times significant deviations are present. The number of patients in whom plasma lipid concentrations shows these significant deviations from normal is summarized in Table VII.

The most significant fact obtained from this analysis is that twenty-five of twenty-seven patients showed an increased percentage of free in total cholesterol. Each of the patients who showed that abnormality had other corroborative evidence of hepatic disease. This evidence exists in the form of positive liver function tests or abnormalities found at operation or necropsy. Roughly, the increased percentage of free

TABLE V

| Author                             | Total   | Cholesterol |      | Per Cent. Free in Total |
|------------------------------------|---------|-------------|------|-------------------------|
|                                    |         | Ester       | Free |                         |
| Gardner (33) and Gainsborough (62) | Female  | —           | 43   | 35                      |
|                                    | 153     |             |      |                         |
|                                    | ± 33    |             |      |                         |
|                                    | Male    |             |      |                         |
| Boyd (16)                          | 169     | —           | 50   | 30                      |
|                                    | ± 41    |             |      |                         |
|                                    | 181     |             |      |                         |
|                                    | ± 22    |             |      |                         |
| Jones                              | 189     | 128         | 53   | 29                      |
|                                    | ± 21    |             |      |                         |
|                                    | 169     |             |      |                         |
|                                    | ± 21    |             |      |                         |
| Sperry (75)                        | 210     | 132         | 57   | 30                      |
|                                    | 215     |             |      |                         |
|                                    | 215     |             |      |                         |
|                                    | 215     |             |      |                         |
| Pinkhardt, Bernhard and Kohn (66)  | 147-404 | 21          | 10   | 23                      |
|                                    | 147-322 |             |      |                         |
|                                    | 147-322 |             |      |                         |
|                                    | 147-322 |             |      |                         |

in total cholesterol corresponded to the degree of hepatic damage. The group of patients who had cirrhosis of the liver usually showed the least change, although as their condition became more critical, changes in the ratio of free to total cholesterol paralleled their clinical condition regardless of whether or not jaundice was present.

In most of these patients who presented increased ratios of free to total cholesterol other factors which, presumably, may have contributed to the effect of the hepatic disease, were found. Fever and anemia were

SUMMARY TABLE VI  
*Plasma lipids*

|                    | Total Lipid | Neutral Fat | Total Fatty Acids | Phospho-Lipid | Total  | Cholesterol Ester | Free   | Per Cent Free in Total |
|--------------------|-------------|-------------|-------------------|---------------|--------|-------------------|--------|------------------------|
| Range              | 1706-289    | 393-50      | 1158-151          | 860-88        | 342-72 | 166-5             | 175-37 | 94-25                  |
| Mean               | 612         | 170         | 368               | 223           | 161    | 89                | 72     | 47                     |
| S. D.              | ± 217       | ± 84        | ± 150             | ± 106         | ± 51   | 42                | ± 27   | ± 18                   |
| Per cent deviation | 35          | 49          | 41                | 47            | 32     | 47                | 38     | 40                     |

*Plasma proteins*

|                    | Total     | Albumin   | Globulin  | Fibrinogen |
|--------------------|-----------|-----------|-----------|------------|
| Range              | 8.80-4.21 | 5.52-1.92 | 4.70-1.76 | 0.82-0.18  |
| Mean               | 6.70      | 3.52      | 3.17      | 0.49       |
| S. D.              | ± 0.86    | ± 0.74    | ± 0.72    | ± 0.17     |
| Per cent deviation | 13        | 21        | 23        | 35         |

outstanding. The lower values for plasma total cholesterol concentration were usually associated with a diminished concentration of plasma albumin. That these changes are not the result of changes in plasma concentration is indicated by the fact that plasma albumin and globulin varied independently. These protein changes may indicate inability of the liver to synthesize plasma albumin or failing nutrition (89, 84, 74, 64, 71).

In contradistinction to the findings of Boyd and Connell (15), only three of this group of patients showed distinct and significant decreases in the concentration of all the plasma lipids. Two of these had cirrhosis of the liver (one of toxic variety, the other Laënnec's type) and the other a toxic hepatitis due to neo-arsphenamine. The disease in all three terminated in death a short while after the discovery of the diminished plasma lipid concentration. Boyd and Connell state that their patients had a variety of dis-

ease conditions affecting the liver, but had no other factor which could contribute to the effect of the specific disease on the concentration of the plasma lipids. Contrariwise, in these three patients in this study, anemia, fever, infection and malnutrition were manifest and must have shared with the liver the role of production of the low level of the plasma lipid concentration. These patients all had marked diminished plasma proteins. It is suggested that nutritional factors exert a very important influence on the production of diminished plasma lipid concentration.

The nature of the plasma lipid changes found in this study are illustrated by the summaries on the studies in four patients. Case 13 was a typical example of Laënnec's type of cirrhosis in whom changes in plasma lipid closely reflected changes in clinical condition of the patient. Case 22 had a toxic hepatitis due to arsphenamine and recovered. Case 23 also had

TABLE VII  
*Number of patients with hepatic disease showing increases in plasma lipids*

|  | Total Lipid | Neutral Fat | Total Fatty Acids | Phospho-lipids | Total | Cholesterol Ester | Free | Per Cent Free in Total Cholesterol |
|--|-------------|-------------|-------------------|----------------|-------|-------------------|------|------------------------------------|
| Beyond range in which 95% of normal values occur | 2           | 6           | 2                 | 8              | 1     | 0                 | 14   | 25                                 |
| Beyond range in which 66% of normal values occur | 7           | 10          | 7                 | 9              | 7     | 2                 | 19   | 25                                 |

*Number of patients with hepatic disease showing decreases in plasma lipids*

|   | Total Lipid | Neutral Fat | Total Fatty Acids | Phospho-lipids | Total | Cholesterol Ester | Free | Per Cent Free in Total Cholesterol |
|---|-------------|-------------|-------------------|----------------|-------|-------------------|------|------------------------------------|
| Below range in which 95% of normal values occur | 3           | 0           | 3                 | 6              | 11    | 15                | 1    | 2                                  |
| Below range in which 66% of normal values occur | 10          | 6           | 7                 | 14             | 19    | 23                | 7    | 3                                  |

**SUMMARY TABLE VIII**  
*Plasma lipids (before operation)*

|                    | Total Lipid | Neutral Fat | Total Fatty Acids | Phospholipid | Total    | Cholesterol Ester | Free     | Per Cent Free in Total |
|--------------------|-------------|-------------|-------------------|--------------|----------|-------------------|----------|------------------------|
| Range              | 2240-447    | 934-19      | 1096-247          | 929-159      | 511-109  | 249-5             | 275-41   | 54-19                  |
| Mean               | 667         | 304         | 616               | 350          | 228      | 100               | 188      | 55                     |
| S. D.              | $\pm 340$   | $\pm 158$   | $\pm 223$         | $\pm 186$    | $\pm 78$ | $\pm 53$          | $\pm 61$ | $\pm 16$               |
| Per cent deviation | 74          | 51          | 37                | 49           | 33       | 53                | 41       | 27                     |

*Plasma proteins (before operation)*

|                    | Total      | Albumin    | Globulin   | Fibrinogen |
|--------------------|------------|------------|------------|------------|
| Range              | 10.23-5.03 | 5.22-1.18  | 4.98-2.17  | 0.57-0.23  |
| Mean               | 6.58       | 3.69       | 2.89       | 0.86       |
| S. D.              | $\pm 0.80$ | $\pm 0.70$ | $\pm 0.56$ | $\pm 0.15$ |
| Per cent deviation | 12         | 21         | 19         | 22         |

a toxic hepatitis due to arsphenamine but died. Case 26 is a typical example of catarrhal jaundice with complete recovery.

#### STUDY OF PLASMA LIPID CONCENTRATION IN PATIENTS WITH OBSTRUCTIVE JAUNDICE

This group is comprised of nineteen patients who had varying degrees of icterus resulting from obstruction to the biliary passages. The obstruction was due to stones in twelve patients; carcinoma of the head of pancreas in three patients; carcinoma of hepatic ducts with secondary liver involvement in two patients; stricture of common duct as well as stones in one patient. In one instance the mechanism producing obstruction could not be determined.

Studies of the plasma lipids and plasma proteins and liver function tests, were executed in this group

in exactly the same manner as in the other two groups.

A summary of the results of all of the plasma lipid and plasma protein determinations made before the obstruction to the outflow of bile was relieved is presented in Table VIII.

A comparison of this summary with that presented in Table I shows that this group is characterized by a statistically significant increase in free cholesterol and an increase in the ratio of free to total cholesterol. The variation which the values of plasma lipid concentrations may undergo is indicated by the percentage by which the standard deviation varies from the mean.

Comparison of this group of values (Table VIII) with the values found in the patients with hepatic diseases (Table I) shows that no difference of statistical significance is present. The wide variation in

**TABLE IX**  
*Number of patients with obstructive jaundice  
Showing increased plasma lipids*

|   | Total Lipid | Neutral Fat | Total Fatty Acids | Phospholipids | Total | Cholesterol Ester | Free | Per Cent Free in Total Cholesterol |
|---|-------------|-------------|-------------------|---------------|-------|-------------------|------|------------------------------------|
| Desired range in which 75% of normal values occur               | 14          | 11          | 14                | 15            | 11    | 2                 | 17   | 18                                 |
| Desired range in which 75% of normal values are expected to lie | 10          | 11          | 17                | 13            | 11    | 2                 | 16   | 19                                 |

*Number of patients with obstructive jaundice  
Showing diminished plasma lipids*

|                                     | Total Lipid | Neutral Fat | Total Fatty Acids | Phospholipids | Total | Cholesterol Ester | Free | Per Cent Free in Total Cholesterol |
|-------------------------------------|-------------|-------------|-------------------|---------------|-------|-------------------|------|------------------------------------|
| Below range of 75% of normal values | 1           | 1           | 1                 | 1             | 1     | 1                 | 1    | 1                                  |
| Above range of 75% of normal values | 7           | 1           | 1                 | 1             | 1     | 1                 | 1    | 1                                  |

values in the two groups renders differentiation on this basis impossible.

Deviations from the range of normal values by individual patients in this group are interesting. The nature and direction of these deviations are summarized in Table IX. Significant is the fact that free cholesterol is increased in all but two patients and cholesterol esters were increased in concentration in only three patients. An increase in total cholesterol concentration, present in only fourteen patients, indicates that the regularity of the increase in free cholesterol is more characteristic than an increase in the total. This finding corresponds with the findings of Bruger and Habs (18), Gardner and Gainsborough (34) and Boyd (14) in clinical patients, and with those of Stern and Suchantke (80) and Chanutin and Ludewig (23) in experimental animals.

An increase in the ratio of free to total cholesterol to a greater or lesser degree is present in every patient studied. This finding is usually explained on the basis of liver damage. That this group of patients had no more liver damage than would be expected in any other group of patients with obstructive jaundice is indicated by the findings at operation and the results of liver function tests. It would seem apparent that excessive liver damage need not be invoked to explain the absence of regular increase of the cholesterol esters in this material. A more likely explanation of the difference probably resides in the differences in the methods of analyses employed by some of the other workers. Moreover, gross alterations in the ratio of free to total cholesterol in the obstructed group did not necessarily indicate a fatal termination as in the patients with hepatic diseases but did reflect the seriousness of the patient's condition. Another noted difference was the fact that diminished concentrations of plasma proteins were not always associated with diminished plasma lipid concentration. Chronicity of obstruction in this material did not produce reduction in the concentration of the plasma lipids despite the fact that marked diminutions in the plasma proteins occurred.

Summaries of the studies of plasma lipid and

plasma protein concentrations after release of the bile duct obstruction are presented in Table X. This summary indicates the tendency of all of the plasma lipids to return to normal. This return to normal concentration is shared by all of the lipids in a qualitative fashion. The wider variation of the free cholesterol and the ratio of free to total cholesterol is probably explainable by the fact that not all patients could be followed until complete recovery occurred.

Three patients' records are presented which are illustrative of the types of changes that occur in plasma lipid concentrations under the influence of obstruction of the bile ducts. Case 36 whose jaundice was due to a common duct stone shows those changes found in uncomplicated obstructive jaundice. This is one of the two patients who showed an increased amount of free cholesterol.

Case 34 had obstructive jaundice due to a carcinoma of the left hepatic duct which at post-mortem examination was found to have extended to involve both ducts. There was minimal hepatic involvement by the carcinoma. The long duration of the jaundice with continuous lipemia is remarkable.

Case 37 shows the characteristic effect on the plasma lipid concentration of chronic low grade obstruction to the common bile duct caused by stricture with an episode of more complete obstruction superimposed. The liver histology in this patient showed the presence of a biliary cirrhosis. It is interesting to note that this patient had a biliary fistula at the time the last plasma lipid study was made. The ratio of free cholesterol to total cholesterol was still increased even though the other liver function studies were negative. This is similar to the finding of Gardner and Gainsborough (34) who report low cholesterol esters in the presence of biliary fistulae.

#### SUMMARY AND CONCLUSIONS

Although the usual response of the plasma lipid concentrations to obstruction of the bile ducts and hepatic disease is in general agreed upon, many investigators arrive at discordant conclusions from their

SUMMARY TABLE X  
*Plasma lipids (after operation)*

|                    | Total lipid | Neutral Fat | Total Fatty Acids | Phospholipid | Total  | Cholesterol |        | Per Cent Free in Total |
|--------------------|-------------|-------------|-------------------|--------------|--------|-------------|--------|------------------------|
|                    |             |             |                   |              |        | Ester       | Free   |                        |
| Range              | 908-413     | 442-76      | 558-224           | 373-100      | 286-94 | 171-15      | 188-38 | 84-29                  |
| Mean               | 612         | 190         | 373               | 203          | 162    | 85          | 77     | 49                     |
| S. D.              | ± 145       | ± 81        | ± 99              | ± 62         | ± 61   | ± 37        | ± 32   | ± 15                   |
| Per cent deviation | 24          | 43          | 27                | 33           | 31     | 44          | 42     | 31                     |

*Plasma proteins (after operation)*

|                    | Total     | Albumin   | Globulin  | Fibrinogen |
|--------------------|-----------|-----------|-----------|------------|
| Range              | 7.40-5.00 | 4.59-2.66 | 4.40-2.01 | 0.85-0.36  |
| Mean               | 6.19      | 3.36      | 2.83      | 0.58       |
| S. D.              | ± 0.76    | ± 0.54    | ± 0.57    | ± 0.12     |
| Per cent deviation | 12        | 16        | 20        | 20         |



studies. Many factors are apparent which probably have contributed to this confusion. Enumerated, these are: attempts to compare results of analyses of whole blood: serum and plasma; the use of methods of widely varying preciseness; failure to adequately control the various studies; failure to realize the wide range of normal concentration of the various lipids especially total cholesterol; failure to recognize the narrow range of variation of the normal ratio of free in total cholesterol; and failure to recognize the non-specific contribution of various physiologic and pathologic factors to the effect on the plasma lipids. A study of plasma lipids concentration in patients with liver diseases and obstructive jaundice has been attempted with the idea of recognizing if unable to control these various factors.

1. The concentration of plasma lipids in normal individuals varies widely in states of health; especially is this true of cholesterol. But despite this wide variation in total cholesterol the ratio of free to total cholesterol varies within very narrow limits.

2. Analyses of serum or plasma with precise methods are necessary to obtain these results.

3. There was no statistically significant difference in the concentration of the plasma lipids of normal subjects and the patients with hepatic diseases studied. However, twenty-five of twenty-seven patients showed an increased percentage of free in total cholesterol and these patients had other corroborative evidence of hepatic damage.

4. Roughly the degree of change in the ratio of free to total cholesterol paralleled the seriousness of the hepatic damage.

5. A lipopenia was not found to be characteristic of the group of patients with hepatic disease. All patients showing a marked lipopenia died. Other factors such as anemia, fever and failing nutrition were present in these patients.

6. The lower concentration of total cholesterol was associated in every instance with diminished plasma albumin concentration.

7. Changes noted are not the results of variation in hemoconcentration since plasma albumin and globulin varied independently under the same conditions.

8. Patients with obstructive jaundice showed a significant increase in the concentration of free cholesterol and an increased percentage of free in total cholesterol.

9. There was no significant difference between the concentration of the plasma lipids of the group of

patients with hepatic disease and those who had obstructive jaundice. Diagnosis was impossible on this basis.

10. The total cholesterol and ester cholesterol did not increase with the same degree of regularity as did the free cholesterol in the presence of obstructive jaundice.

11. Diminished plasma albumin concentration was not necessarily associated with diminished cholesterol concentration in the patients with obstructive jaundice.

12. Gross changes in the ratio of free to total cholesterol in patients with obstructive jaundice did not always indicate a fatal termination as in the patients with hepatic diseases.

13. Great care must be exercised in the interpretation of results of lipid determination since many factors, such as fever, anemia, malnutrition, etc., may play a part in producing noted changes.

14. It is suggested that malnutrition is an important but not the only factor in the production of lipopenic states in hepatic disease.

Grateful acknowledgement is made to Dr. George M. Piersol, Dr. H. L. Bockus, and Dr. J. Frederick Monaghan, who permitted the use of their patients in this study.

#### REPORT OF CASES

Case 13. C. W. White, male, age 43. History dates from February, 1938, when the patient had an attack of jaundice associated with right lower quadrant pain. He was hospitalized at that time for one month during which the jaundice subsided. For years previous to the attack of jaundice he had been a generous consumer of alcohol. In February, 1939, he again began to have a swollen abdomen. In August, 1939, he had two abdominal paracenteses done. Stools have always been normal in color. Blood pressure 118/65. There was no visible jaundice. The liver extended 4.5 cm. below the costal margin, and the spleen was palpable. He was moderately anemic. The erythrocytes ranged between 3.28 and 3.99 million and the hemoglobin from 9.5 to 11 grams. Stools were grossly colored with bile. He was treated with a high carbohydrate diet with extra glucose feedings, bile salts, liver extract, vitamins, repeated transfusions, and diuretics. Fluid was removed from his abdomen on four occasions. Felt fairly well until 11/2/39 when he began to have nausea, and on 11/19/39 he vomited large quantities of bright red clotted blood. This bleeding was found to be associated with a prothrombin of 14 per cent. (The patient was not syphilitic). Death occurred on 11/20/39. Throughout the period of hospitalization the patient was febrile with temperature ranging from 99 to 104 degrees.

#### CASE 13

| T.L. | N.F. | T.F.A. | Pl. | T.C. | E.C. | F.C. | % F.C. | Date     | V.  | B. | U.    | Miscellaneous |
|------|------|--------|-----|------|------|------|--------|----------|-----|----|-------|---------------|
|      |      |        |     |      |      |      |        | 9-2-39   | 0.5 |    |       |               |
| 427  | 121  | 252    | 124 | 128  | 81   | 47   | 38     | 9-5-39   | —   | 30 | 1/500 |               |
| 407  | 125  | 242    | 112 | 122  | 71   | 51   | 42     | 9-12-39  |     |    |       |               |
|      |      |        |     |      |      |      |        | 9-18-39  |     |    | 1/300 |               |
| 458  | 188  | 310    | 123 | 128  | 83   | 45   | 35     | 9-23-39  |     |    |       |               |
| 566  | 222  | 343    | 151 | 162  | 46   | 116  | 72     | 10-6-39  |     |    |       |               |
| 599  | 165  | 340    | 193 | 147  | 90   | 57   | 39     | 10-24-39 |     |    |       |               |
| 519  | 191  | 325    | 180 | 125  | 35   | 90   | 72     | 11-16-39 |     |    |       |               |

Case 22. A. P. Negro, male, age 25. This patient had a penile lesion at the age of 17 years. Serologic studies were positive for syphilis about three weeks before his admission on 3/31/39. He received two injections of Neo-arsphenamine in the next two weeks after finding of the positive tests for syphilis. After the first injection the patient began to have upper abdominal pain associated with nausea and vomiting but no diarrhea. He began to become jaundiced at the same time. He had one injection of the arsenical after the jaundice developed. On admission the patient was found to be deeply jaundiced but had no detectable enlargement of the liver or spleen. Feces obtained by digital examination was light in color. Duodenal intubation on 4/1/39 and again on 4/4/39 showed a free flow of bile. At the latter date the serum bilirubin was rapidly diminishing. Patient was discharged on 4/5/39 and followed in the out-patient clinic. His red cell count was 4.2 million cells, and the hemoglobin 11.5 grams.

not change. During her stay in the hospital her red cell count was on two occasions over four million and the hemoglobin 11.5 grams. Throughout her stay in the hospital she was febrile. The temperature fluctuations varied between 99 and 100 degrees until the last three days of life when the temperature rose to 101 to 103 degrees. On examination there was enlargement of the liver but the spleen was not felt. Patient died 10/1/39. No autopsy was done. The clinical diagnosis was syphilis, toxic hepatitis due to arsenic.

Case 26. B. D. White, female, age 24. Admitted 4/23/39. Discharged 5/6/39 as improved. Onset of symptoms occurred 4/19/39 with upper respiratory infection. Following this, bowel irregularity developed. This latter symptom was associated with left upper quadrant pain. Dark urine was noted 4/24/39. Icterus appeared 4/25/39. On this same date some splenic enlargement was found. The

## CASE 22

| T.L. | N.F. | T.F.A. | Pl. | T.C. | E.C. | F.C. | % F.C. | Date    | V.   | B. | U.    | Miscellaneous           |
|------|------|--------|-----|------|------|------|--------|---------|------|----|-------|-------------------------|
| 1706 | 393  | 1155   | 860 | 342  | 167  | 175  | 51     | 3-31-39 |      |    |       | Phosphatase 3.56 units  |
|      |      |        |     |      |      |      |        | 4-1-39  | 18.0 | —  | 1/100 | Galactose 0.197 gms.    |
|      |      |        |     |      |      |      |        | 4-4-39  | 8.5  | 30 | 1/160 |                         |
|      |      |        |     |      |      |      |        | 4-5-39  |      |    |       | Hippuric acid 4.25 gms. |
| 899  | 196  | 511    | 333 | 267  | 154  | 113  | 42     | 4-11-39 | 2.4  | —  | —     |                         |
|      |      |        |     |      |      |      |        | 4-15-39 | 2.1  | 10 | 1/20  |                         |
| 629  | 113  | 364    | 256 | 174  | 119  | 55   | 32     | 4-22-39 | 0.9  | 8  | 1/20  |                         |
|      |      |        |     |      |      |      |        | 4-29-39 | 0.4  | 6  | 1/20  |                         |
| 573  | 166  | 347    | 163 | 164  | 119  | 45   | 27     | 5-6-39  | 0.4  | 4  | 1/20  |                         |
|      |      |        |     |      |      |      |        | 5-20-39 | 0.3  | 0  | 1/20  |                         |
|      |      |        |     |      |      |      |        | 5-27-39 | 0.2  | 4  | 1/20  |                         |

Temperature while in the hospital varied between 98 and 99 degrees. His therapy consisted largely of a diet high in carbohydrate reinforced with extra sugar, bile salts, limitations of fat intake. The clinical diagnosis in this case was: syphilis, toxic hepatitis due to arsenic.

Case 23. V. W. Negro, female, age 32. This patient is known to have had syphilis for several years. She had a total of 30 injections of bismuth before she was started on Neo-Arsphenamine on 7/13/39. Following the first injection of this compound she began having upper abdominal pain associated with nausea and vomiting. Several days later she noted that her eyes were icteric. Following the appearance of the jaundice she had three injections of 0.3 gram of Neo-Arsphenamine and one of 0.15 gram. The jaundice deepened during this time and the abdominal pain and nausea and vomiting became more severe until she was unable to retain anything but liquid food at the time of her admission 9/14/39. The color of the stools did

jaundice subsided and patient discharged. This was typically a case of Acute Catarrhal Jaundice.

Case 34. J. M. White, female, age 50. Painless jaundice associated with clay colored stools and dark urine developed in this patient about 10/1/38. The jaundice unrelentingly became more intense until the time of her admission 11/14/38. After study she was explored 11/23/38. At operation a primary carcinoma of the left hepatic duct was found. This had extended so that there was minimal liver involvement, but the other duct was almost completely occluded. No surgical relief of the obstruction was attempted. This patient lived approximately six and one-half months after the exploration and died 5/28/39. Ascites and edema developed a short while before death. The abdomen was tapped several times for relief. Bile appeared in the stool for a short while about two months after the operation at which time there was a marked diminution in the level of the serum bilirubin. From time to time

## CASE 23

| T.L. | N.F. | T.F.A. | Pl. | T.C. | E.C. | F.C. | % F.C. | Date    | V.   | B. | U.    | Miscellaneous         |
|------|------|--------|-----|------|------|------|--------|---------|------|----|-------|-----------------------|
| 675  | 174  | 391    | 273 | 184  | 65   | 119  | 64     | 9-15-39 | 11.0 | —  | —     |                       |
|      |      |        |     |      |      |      |        | 9-18-39 | 16.0 | —  | 1/600 | Phosphatase 7.4 units |
|      |      |        |     |      |      |      |        | 9-19-39 | —    | —  | —     | Galactose 7.32 grams  |
|      |      |        |     |      |      |      |        | 9-22-39 | 12.0 | —  | 1/400 |                       |
| 468  | 100  | 282    | 282 | 86   | 5    | 81   | 94     | 9-23-39 |      |    |       |                       |
| 316  | 33   | 161    | 180 | 93   | 15   | 78   | 84     | 9-26-39 |      |    |       |                       |
| 323  | 127  | 204    | 123 | 72   | 10   | 62   | 86     | 9-29-39 |      |    |       |                       |



## CASE 26

| T.L. | N.F. | T.F.A. | Pl. | T.C. | E.C. | F.C. | % F.C. | Date     | V.   | B. | Galactose |
|------|------|--------|-----|------|------|------|--------|----------|------|----|-----------|
| 668  | 259  | 431    | 198 | 158  | 79   | 79   | 50     | 4-26-39  | 4.3  | —  | —         |
|      |      |        |     |      |      |      |        | 4-28-39  | 6.0  | —  | 4.6       |
|      |      |        |     |      |      |      |        | 5-1-39   | 4.5  | —  | 4.0       |
|      |      |        |     |      |      |      |        | 5-3-39   | 3.4  | —  | —         |
| 627  | 141  | 335    | 224 | 190  | 107  | 83   | 41     | 5-5-39   | 2.1  | —  | 2.26      |
| 740  | 208  | 441    | 213 | 217  | 149  | 68   | 31     | 5-11-39  | 1.25 | 12 | —         |
| 790  | 218  | 475    | 246 | 223  | 155  | 68   | 30     | 5-18-39  | 0.6  | —  | —         |
|      |      |        |     |      |      |      |        | 6-29-39  | 0.25 | —  | —         |
|      |      |        |     |      |      |      |        | 8-8-39   | 0.2  | —  | —         |
|      |      |        |     |      |      |      |        | 10-17-39 | 0.2  | —  | —         |

## CASE 34

| T.L. | N.F. | T.F.A. | Pl. | T.C. | E.C. | F.C. | % F.C. | Date     | V.   | B. | U. | Miscellaneous       |
|------|------|--------|-----|------|------|------|--------|----------|------|----|----|---------------------|
|      |      |        |     |      |      |      |        | 11-15-38 |      |    | 0  | Galactose 4.21 gms. |
|      |      |        |     |      |      |      |        | 11-17-38 | 8.2  | —  | 0  |                     |
|      |      |        |     |      |      |      |        | 11-19-38 | 17.0 | —  | —  |                     |
|      |      |        |     |      |      |      |        | 11-28-38 | 15.0 | —  | —  |                     |
|      |      |        |     |      |      |      |        | 12-23-38 | 27.0 | —  | —  |                     |
|      |      |        |     |      |      |      |        | 1-9-39   | 14.0 | —  | —  |                     |
|      |      |        |     |      |      |      |        | 1-31-39  | 12.0 | —  | —  |                     |
|      |      |        |     |      |      |      |        | 2-7-39   | 14.0 | —  | —  |                     |
|      |      |        |     |      |      |      |        | 2-14-39  | 12.0 | —  | —  |                     |
| 1283 | 300  | 792    | 657 | 255  | 92   | 163  | 64     | 2-20-39  | 16.0 | —  | —  |                     |
| 1437 | 509  | 951    | 554 | 282  | 19   | 263  | 93     | 3-9-39   | 7.8  | —  | —  |                     |
| 1250 | 322  | 750    | 590 | 288  | 74   | 214  | 74     | 4-6-39   | 12.0 | —  | —  |                     |
| 1212 | 377  | 730    | 512 | 293  | 45   | 248  | 85     | 4-24-39  | 16.0 | —  | —  |                     |
| 2007 | 933  | 1406   | 713 | 313  | 66   | 251  | 67     | 5-5-39   | 19.0 | —  | —  |                     |

## CASE 36

| T.L. | N.F. | T.F.A. | Pl. | T.C. | E.C. | F.C. | % F.C. | Date    | V.   | B. | U.    | Miscellaneous                         |
|------|------|--------|-----|------|------|------|--------|---------|------|----|-------|---------------------------------------|
|      |      |        |     |      |      |      |        | 3-28-39 | 6.0  | —  | —     | Galactose 1.8 gms.                    |
|      |      |        |     |      |      |      |        | 3-29-39 | —    | —  | —     |                                       |
|      |      |        |     |      |      |      |        | 3-31-39 | 15.0 | —  | —     | Galactose 5.6 gms.                    |
|      |      |        |     |      |      |      |        | 4-3-39  | 17.5 | —  | —     |                                       |
|      |      |        |     |      |      |      |        | 4-4-39  | —    | —  | 1.390 | Urobilinogen 23.4 mg. excreted daily. |
| 2250 | 642  | 1383   | 939 | 511  | 236  | 275  | 54     | 4-6-39  | —    | —  | —     |                                       |
|      |      |        |     |      |      |      |        | 4-8-39  | 8.1  | —  | —     |                                       |
|      |      |        |     |      |      |      |        | 4-11-39 | 8.7  | —  | —     |                                       |
|      |      |        |     |      |      |      |        | 4-13-39 | 5.3  | —  | —     |                                       |
| 1468 | 337  | 816    | 493 | 471  | 249  | 222  | 47     | 4-14-39 | —    | —  | —     |                                       |
|      |      |        |     |      |      |      |        | 4-15-39 | 1.7  | —  | —     |                                       |
|      |      |        |     |      |      |      |        | 4-18-39 | 2.5  | —  | —     |                                       |
|      |      |        |     |      |      |      |        | 4-19-39 | 2.0  | —  | —     |                                       |
| 738  | 137  | 404    | 256 | 237  | 161  | 76   | 34     | 4-22-39 | 1.7  | —  | —     |                                       |
| 854  | 290  | 558    | 298 | 192  | 110  | 82   | 43     | 4-27-39 | 0.7  | —  | —     |                                       |
| 729  | 209  | 442    | 250 | 194  | 114  | 80   | 41     | 5-4-39  | —    | —  | —     |                                       |
|      |      |        |     |      |      |      |        | 5-11-39 | 0.9  | —  | —     |                                       |
| 634  | 191  | 392    | 193 | 168  | 122  | 46   | 27     | 5-19-39 | —    | —  | —     |                                       |

during the period after operation, this patient showed evidences of minor bleeding that was associated with marked reduction in prothrombin. By 5/6/39 she was bleeding rather profusely from most of the mucous membranes, namely, buccal mucosa, vaginal mucosa, and intestinal tract. She had no anemia at the time of her admission but late in the course of the illness a progressive hypochromic anemia appeared. Her red cell count was 3 million on 3/23/39 and 2.5 million on 5/2/39. This patient was continuously febrile for the entire post-operative period with daily temperature fluctuations that ranged between 99 and 103 degrees, except for the last two weeks of her life when her temperature was recorded as being generally below 99 degrees. A necropsy was performed.

Case 36. T. F. White, male, age 39. Admitted 3-24-39. This patient has had repeated attacks of typical biliary colic for over a year. During previous hospital admissions he has had a positive clinical diagnosis of cholecystitis and cholelithiasis made on the basis of clinical and X-ray examination. Such an attack of biliary colic occurred three days before admission following which he became slightly jaundiced. On examination at the time of admission the patient was found to be slightly overweight, and the skin and mucous membrane were deeply jaundiced. After the jaundice had subsided somewhat his abdomen was explored on 4/20/39. At this time a large stone was found in the dilated common duct. The liver was normal in size and no evidence of cirrhosis could be felt or seen. A cholecystectomy was done at that time and a T-tube was

placed in the common duct. He made an uneventful recovery. At no time was the patient's blood count below normal. There was no serologic evidence of syphilis. During the period before operation the patient was afebrile, and after operation fever occurred only on the first three post-operative days. He was discharged 5/15/39.

Case 37. J. C. White, female, age 64. This patient has a history of biliary tract disease dating back to 1920 when a cholecystectomy was done for the removal of numerous gall stones. During this operation the common duct was severed and an end to end anastomosis was made. She became jaundiced again a short while later and was re-operated upon for removal of small common duct stones. Since that time she has had repeated attacks of upper right quadrant pain with low grade jaundice. She has been studied in the Graduate Hospital numerous times since 1933. She was last admitted 9/15/39, following an attack of severe upper right quadrant pain and jaundice. Examination at the time of admission showed visible jaundice. Her liver was palpable about 5 cm. below the right costal border and the spleen could not be felt. After a period of study, the result of which was the conclusion that she must have residual common duct stones, her icterus became more marked. Without further delay to allow the jaundice to subside, she was explored 10/9/39. This step was taken because of the fear of more severe liver damage in this individual incident to the increased jaundice. At operation a stricture of the common bile duct was found which had a lumen about 1 mm. in diameter.

# CASE 37

| T.L. | N.F. | T.F.A. | Pl. | T.C. | E.C. | F.C. | % F.C. | Date     | V.   | B. | U.   | Miscellaneous       |
|------|------|--------|-----|------|------|------|--------|----------|------|----|------|---------------------|
| 567  | 166  | 345    | 137 | 168  | 113  | 55   | 33     | 5-28-39  | 1.8  | 25 | 1.20 |                     |
| 804  | 219  | 510    | 383 | 156  | 69   | 87   | 56     | 9-16-39  |      |    |      |                     |
|      |      |        |     |      |      |      |        | 9-19-39  | 5.6  | 55 | —    |                     |
| 1210 | 423  | 514    | 543 | 200  | 66   | 134  | 67     | 9-25-39  | —    | —  | —    |                     |
|      |      |        |     |      |      |      |        | 9-26-39  | 7.0  | 60 | 1.20 |                     |
| 730  | 153  | 454    | 363 | 205  | 102  | 103  | 51     | 9-28-39  |      |    |      |                     |
|      |      |        |     |      |      |      |        | 10- 3-39 | 9.0  | —  | —    |                     |
| 747  | 319  | 506    | 267 | 136  | 38   | 98   | 73     | 10- 5-39 | —    | —  | —    | Galactose 0.302 gm. |
| 814  | 349  | 556    | 313 | 136  | 24   | 112  | 82     | 10- 7-39 |      |    |      |                     |
| 704  | 335  | 470    | 176 | 162  | 61   | 101  | 63     | 10- 8-39 | 14.0 | —  | —    |                     |
| 658  | 313  | 456    | 210 | 116  | 28   | 88   | 76     | 10-11-39 | 18.0 | —  | —    |                     |
|      |      |        |     |      |      |      |        | 10-12-39 | 22.0 | —  | —    |                     |
| 656  | 392  | 490    | 160 | 94   | 15   | 79   | 84     | 10-13-39 | 26.0 | —  | —    |                     |
|      |      |        |     |      |      |      |        | 10-14-39 | 12.0 | —  | —    |                     |
| 652  | 442  | 498    | 100 | 98   | 18   | 80   | 82     | 10-15-39 | 7.0  | —  | —    |                     |
| 567  | 318  | 412    | 127 | 97   | 37   | 60   | 62     | 10-16-39 | 2.5  | —  | —    |                     |
| 468  | 193  | 309    | 127 | 107  | 61   | 46   | 43     | 10-19-39 | 2.5  | —  | —    |                     |
| 476  | 154  | 299    | 163 | 115  | 66   | 49   | 43     | 10-24-39 | 0.6  | —  | —    |                     |
| 422  | 114  | 255    | 149 | 111  | 71   | 40   | 36     | 10-28-39 | —    | —  | —    |                     |
| 509  | 159  | 315    | 162 | 132  | 84   | 48   | 36     | 11- 6-39 | —    | —  | —    |                     |
|      |      |        |     |      |      |      |        | 11-17-39 | 0.7  | —  | —    |                     |
| 477  | 188  | 311    | 135 | 112  | 62   | 50   | 45     | 11-18-39 | —    | —  | —    |                     |
|      |      |        |     |      |      |      |        | 11-27-39 | 0.5  | —  | —    |                     |
|      |      |        |     |      |      |      |        | 11-28-39 | 1.2  | —  | —    |                     |
| 461  | 165  | 285    | 131 | 124  | 61   | 63   | 51     | 11-29-39 | —    | —  | —    |                     |
|      |      |        |     |      |      |      |        | 12- 5-39 | 0.3  | 3  | 1.80 |                     |
| 507  | 144  | 302    | 168 | 142  | 79   | 63   | 44     | 12-14-39 | —    | —  | —    |                     |
|      |      |        |     |      |      |      |        | 12-16-39 | 0.2  | 4  | 0    |                     |

Proximal to the stricture there were hundreds of small pigment stones of which none was larger than the size of a pea. A plastic operation was done on the common duct and a T-tube sewn in place. As many of the small stones in the hepatic ducts were aspirated. A biopsy of the liver was made. Post-operatively there was a marked increase

in the jaundice for a period of four days after which the jaundice began to clear. This patient had no evidence of syphilis or diabetes. Her red cell count was maintained between 3.8 to 4.5 million. During the post-operative period she was febrile throughout her stay in the hospital. At the time of discharge the T-tube was still in place.

## REFERENCES

- Adler, A. and Lemmel, H.: Zur feineren Diagnostik der Leberkrankheiten. 1. Cholesterin-Ester im Blutes. *Leberkrankh. D. Arch. klin. Med.*, 158:173-214, Jan., 1928.
- Bang, I.: Über Cholesterinämie. *Biochem. Ztschr.*, 91:122-127, Sept., 1918.
- Beumer, H. and Burger, M.: Beiträge zur chemie des Blutes in Krankheiten mit besonderer Berücksichtigung des Lipoids. *Ztschr. für exper. Path. u. Therap.*, 13:343-361, May, 1913.
- Bing, H. J. and Heckscher, A.: 11 Mitteilung: Über die Fettmenge des Blutes bei normalen menschen. *Biochem. Ztschr.*, 141:53, 1921.
- Blix, G.: Diabetic Lipemia. 1. *Acta. Med. Scandinav.*, 64:142-259, 1926.
- Bloor, W. R.: The Distribution of the Lipoids ("Fats") in Human Blood. *J. Biol. Chem.*, 25:417, Sept., 1916.
- Bloor, W. R.: Determination of Small Amounts of Lipid in Blood Plasma. *J. Biol. Chem.*, 77:53-73, April, 1928.
- Bloor, W. R.: Oxidation Determination of Phospholipid Lecithin and Cephalin in Blood Tissues. *J. Biol. Chem.*, 82:273-286, May, 1929.
- Boyd, E. M.: A Differential Lipid Analysis in Normal Young Women by Micro-oxidation Methods. *J. Biol. Chem.*, 101:323-336, June, 1933.
- Boyd, E. M.: The Lipopenia of Fever. *Canad. M. A. J.*, 32:500-506, May, 1935.
- Boyd, E. M.: Diurnal Variations in Plasma Lipids. *J. Biol. Chem.*, 110:61-70, June, 1935.
- Boyd, E. M.: Anesthesia and Blood Lipids. *S. G. O.*, 62:577-683, April, 1936.
- Boyd, E. M.: The Extraction of Blood Lipids. *J. Biol. Chem.*, 114:223-234, May, 1936.
- Boyd, E. M.: The Oxidative Micro Estimation of Blood Lipids. *Am. J. Clin. Path. Tech. Suppl.*, 2:77-90, May, 1938.
- Boyd, E. M. and Connell, W. F.: Lipopenia Associated with Cholesterol Estersturz in Parenchymatous Hepatic Disease. *Arch. Int. Med.*, 61:755-761, May, 1938.
- Boyd, E. M. and Murray, R. B.: Effects of Anti-coagulants on Blood Lipids. *J. Biol. Chem.*, 117:629-638, 1937.
- Brin, G. C.: Cholesterol Content of the Red Blood Cells in Man. *Acta. Med. Scandinav. Suppl.*, 99:3-237, 1939.
- Drüger, M. and Habs, H.: Über Die Veresterung des Serumcholesterins bei Leberkrankheiten. *Klin. Wochenschr.*, 6:2221-2223, Nov. 1927.
- Campbell, W. R. and Hanna, M. S.: The Determination of Nitrogen by Modified Kjeldahl Methods. *J. Biol. Chem.*, 119:107, June, 1937.
- Campbell, W. R. and Hanna, M. S.: The Albumins, Globulins and Fibrinogen of Serum and Plasma. *J. Biol. Chem.*, 119:15-33, June, 1937.
- Campbell, W. R. and Hanna, M. S.: Sulfites as Protein and Precipitants. *J. Biol. Chem.*, 119:9-14, June, 1937.
- Chaufford, A., Laroche, G. and Grigaut, A.: De la teneur en Cholesterines des capsules surrenales dans differents etats Pathologiques. *Compt. rend. Soc. de biol.*, 73:23-25, July, 1912.
- Chanutlin, A. and Ludewig, S.: The Blood Plasma Cholesterol and Phospholipid Phosphorus in Rats Following Partial Hepatectomy and Following Ligation of the Bile Duct. *J. Biol. Chem.*, 115:1-14, 1936.
- Dennis, W.: Cholesterol in Human Blood Under Pathological Conditions. *J. Biol. Chem.*, 29:93-110, Feb., 1917.
- Epstein, E. Z.: Cholesterol of the Blood Plasma in Biliary and Hepatic Disease. *Arch. Int. Med.*, 60:203-222, Aug., 1932.
- Epstein, E. Z. and Greenspan, E. B.: Chemical Significance of Cholesterol Partition of the Blood Plasma in Hepatic and Biliary Diseases. *Arch. Int. Med.*, 68:660, 1936.
- Feigl, J.: Untersuchungen über akute gelbe Leberstrophie. 111—Fette und Lipoids des Blutes. *Biochem. Ztschr.*, 86:1-47, March, 1938.
- Feigl, J.: Über das Vorkommen und die Verteilung von Fetten und Lipoiden in menschlichen Blutplasma bei Ikterus und Cholemie. Chemische Beiträge zur Kenntnis spezifischer Lipämien. III. *Biochem. Ztschr.*, 90:1-38, Sept., 1918.
- Feigl, J.: Ueber das Vorkommen und die Verteilung von Fetten und Lipoiden in menschlichen Blut bei Toxämien. (hamatnämischen) Krankheitszuständen. Beobachtungen bei Pernizien Anämie und hamalytischen Ikterus) Chemische Beiträge zur Kenntnis des Lipemegabietes, VI. *Biochem. Ztschr.*, 93:94-275, 1919.
- Folch, Schneider and Van Slyke, D. D.: *J. Biol. Chem.*, 133 (Proc.) xxxii, May, 1940.
- Gardner, J. A. and Fox, F. W.: A Critical Study of the Methods of Estimating Cholesterol and its Esters in Tissues. *Biochem. J.*, 18:1058-1059, 1924.
- Gardner, J. A. and Gainsborough, H.: Cholesterol Secretion in Urine. 1. *Biochem. J.*, 19:667-671, 1925.
- Gardner, J. A. and Gainsborough, H.: Studies on the Cholesterol Content of Normal Human Plasma; on the So-Called Alimentary Hypercholesterolemia. *Biochem. J.*, 22:1048-1056, 1928.
- Gardner, J. A. and Gainsborough, H.: Blood Cholesterol Studies in Biliary and Hepatic Disease. *Quart. J. Med.*, 23:465-483, July, 1930.
- Gardner, J. A. and Williams, M.: A Critical Study of the Methods of Estimating Cholesterol and Allied Substances. *Biochem. J.*, 15:363-375, 1921.
- Gildea, E. F., Kohn, E. and Man, E. B.: The Relationship Between Body Build and Serum Lipoids and a Discussion of These Qualities as Pkynophilic and Lipoophilic Factors in Structure of Personality. *Am. J. Psychiat.*, 92:1247-1250, May, 1936.
- Gildea, E. F., Mann, E. B. and Biach, R. W.: Long Term Study of the Variations in Serum Proteins, Non Protein Nitrogen, and Lipoids in Patients with Schizophrenic and Manic Depressive Psychoses and Normal People. *Arch. Neurol. and Psychiat.* Cited by Man, Gildea and Peters (92).
- Grigaut, A. et L'Huillier, A.: Iaux compare de la cholesterin des hematies et du serum dans le sang normal a pathologique. *Compt. rend de Soc. Biol.*, 73:202-203, July, 1912.
- Hawkins, W. B. and Wright, A.: The Blood Plasma Cholesterol; Fluctuations Due to Liver Injury and Bile Duct Obstruction. *J. Exper. Med.*, 59:427-439, April, 1934.
- Jezler, A.: Cholesterinbestimmungen in Blut als Leberfunktionsprüfung. *Schweiz. med. Wochenschr.*, 68:108-110, Jan. 29, 1938.
- Jones, C. A.: A Clinical and Laboratory Study of Plasma Lipids in Obstructive Jaundice and Parenchymatous Hepatic Disease. Thesis, Graduate School of Medicine, University of Pennsylvania, 1941.
- Kelsey, F. E.: Determination of Cholesterol. *J. Biol. Chem.*, 127:15-22, Jan., 1939.
- Lehnher, E. R.: The Value of Icteric Indices and Plasma Lipids in the Diagnosis of Jaundice. *New England J. Med.*, 211:467-492, Sept. 11, 1934.
- Luden, G.: Observation on Cholesterol Retention as a Factor in Cell Proliferation. *J. Lab. and Clin. Med.*, 1:662-676, June, 1916.
- Luden, G.: Studies on Cholesterol. 111—The Influence of Bile Derivatives in Blood's Cholesterol Determination. (Preliminary Report). *J. Biol. Chem.*, 29:463-475, April, 1917.
- Man, E. B. and Gildea, E. F.: A Modification of the Stoddard and Drury Titrimetric Method for the Determination of the Fatty Acids in Blood Serum. *J. Biol. Chem.*, 59:43-60, Dec., 1932.
- Man, E. B. and Gildea, E. F.: Serum Lipoids in Malnutrition. *J. Clin. Invest.*, 15:205-211, March, 1936.
- Man, E. B. and Gildea, E. F.: Variations in Lipemia of Normal Subjects. *J. Biol. Chem.*, 119:768-779, July, 1937.
- Mann, E. B. and Peters, J. P.: Gravimetric Determination of Serum Cholesterol Adapted to the Man and Gildea Fatty Acid Method with a Note on the Estimation of Lipoid Phosphorus. *J. Biol. Chem.*, 101:685-696, Apr., 1933.
- Man, E. B. and Peters, J. P.: Serum Lipoids in Diabetes. *J. Clin. Invest.*, 14:579-594, Sept., 1935.
- Mancke, R.: Studien über den Cholesterinstoffwechsel 11—Mittelunr. Der Cholesteringehalt des Blutes bei Leberkrankheiten. *Deutsches Arch. für klin. Med.*, 170:355-368, March, 1931.
- Maschnikov, A. L.: Über Die Rolle Der Leber in Cholesterinstoffwechsel. *Deutsches Klin. Wochenschr.*, 11:1910-1912, Nov., 1932.
- Mueller, J. H.: A Comparison of Results Obtained by Colorimetric and Gravimetric Determination of Cholesterol. *J. Biol. Chem.*, 25:549, 1916.
- Mueller, J. H.: A Note on Solubility of Cholesterol Dicitonide. *J. Biol. Chem.*, 30:39-40, May, 1917.
- Müllbeck, O. and Kaufman, C.: Die gravimetrische Cholesterinbestimmung im Blut und Serum. *Biochem. Ztschr.*, 233:222-235, April, 1931.
- Müllbeck, O. and Kaufman, C.: Die cholesteringehalt im Blut und Serum bei gesunden Frauen in den verschiedenen Lebenszeiten und seiner Beziehungen zur Sexualfunktion. *Ztschr. f. d. Gesam. exper. Med.*, 102:461-468, Feb., 1938.
- Nachlas, A., Duff, G. L., Tidwell, H. C. and Holt, L. E., Jr.: Liver Function as Tested by the Lipemic Curve After Intravenous Fat Administration. *J. Clin. Invest.*, 15:149-151, Jan., 1936.
- Okey, R.: Micro Method for Estimation of Cholesterol by Oxidation of Dicitonide. *J. Biol. Chem.*, 88:367-379, Aug., 1930.
- Okey, R. and Boyden, R. E.: Studies in Metabolism in Women. III. Variation in the Lipid Content of Blood in Relation to the Menstrual Cycle. *J. Biol. Chem.*, 72:261-281, March, 1927.
- Okey, R. and Stewart, D.: Diet and Blood Cholesterol in Normal Women. *J. Biol. Chem.*, 99:717-727, Feb., 1933.
- Oser, B. L. and Karr, W. G.: The Lipoid Partition in Blood in Health and in Disease. *Arch. Int. Med.*, 37:507-515, Oct., 1925.
- Page, S. H., Farr, L. E. and Weech, A. A.: The Effect of Prolonged Low Protein Diet on the Serum Lipoids of Dogs. *J. Biol. Chem.*, 121:111-116, Oct., 1937.
- Page, S. H., Kirk, E., Lewis, W. H., Thompson, W. R. and Van Slyke, D. D.: Plasma Lipids of Normal Men at Different Ages. *J. Biol. Chem.*, 111:613-639, Nov., 1935.
- Peters, J. P. and Eisenman, A. J.: The Serum Proteins in Disease Not Primarily Affecting the Cardiovascular System or Kidneys. *Am. J. Med. Sci.*, 186:809-833, Dec., 1933.
- Peters, J. P. and Van Slyke, D. D.: Quantitative Clinical Chemistry. Vol. I. Interpretations pp. 218-265. William Wilkins & Co., Baltimore, 1931.
- Pinkhart, O. C., Bernhard, A. and Kohn, S. L.: The Significance of the Cholesterol Partition of the Blood Serum in Surgery of the Gall Bladder. *Am. Surg.*, 110:701-719, Oct., 1939.
- Rakestraw, N. W.: Clinical Factors in Fatigue. I. The Effect of Muscular Exercise on Certain Common Blood Constituents. *J. Biol. Chem.*, 47:565, Aug., 1921.
- Rakestraw, N. W., Berley, C. V. and Hohn, Y. D.: Chemical Factors in Fatigue: Further Changes in Blood Constituents Following Strenuous Muscular Exercise. *J. Biol. Chem.*, 121:124, May, 1923.
- Reinhold, J. G.: The Determination of Cholesterol. II. Factors Influencing the Accuracy of Various Methods. *Am. J. Clin. Path.*, 6:31-40, Jan., 1936.
- Rothschild, M. A. and Felson, J.: Cholesterol Content of Blood

- in Various Hepatic Conditions. *Arch. Int. Med.*, 24:520-522, Nov., 1919.
71. Saltesen, H. A.: Variations in the Plasma Proteins in Non-renal Conditions. *Acta. Med. Scandinav.*, 72:113-123, 1929.
  72. Shuy, H. and Fiemann, P.: The Value of a Combined Study of the Newer Laboratory Tests in the Differential Diagnosis of Toxic and Obstructive Jaundice Including Blood Phosphatase, Cholesterol, Galactose Tolerance and Glucose Tolerance. *Am. J. Dig. Dis.*, 5:597-606, Nov., 1938.
  73. Smith, R. M. and Marble, A.: The Colorimetric Determination of Free and Combined Cholesterol. *J. Biol. Chem.*, 117:673-684, Feb., 1937.
  74. Snell, A. M.: The Effects of Chronic Disease of the Liver on the Composition and Physicochemical Properties of Blood. Changes in the Serum Proteins, and Reduction in the Oxygen Saturation of Arterial Blood. *Ann. Int. Med.*, 9:690-711, Dec., 1935.
  75. Sperry, W. M.: The Relationship Between Total and Free Cholesterol in Human Blood Serum. *J. Biol. Chem.*, 111:125-131, May, 1936.
  76. Sperry, W. M.: The Concentration of Total Cholesterol in the Blood Serum. *J. Biol. Chem.*, 117:391-395, Jan., 1937.
  77. Sperry, W. M. and Schoenhiermer, R.: Comparison of Serum, Heparinized Plasma, and Oxalated Plasma in Regard to Cholesterol Content. *J. Biol. Chem.*, 110:655-658, Aug., 1935.
  78. Stepp, W.: Über den Verhältnissen des Blutecholsterins beim Ikterus. *Beitr. Pathol. Anat. U. Z. allg. Pathol.*, 69:233-241, 1921.
  79. Stepp, W.: Über den Cholesteringehalt des Bluteserums bei Krankheiten. *Munch. med. Wochenschr.*, 65:781-783, July, 1931.
  80. Stern, R. and Suchanek, G.: Clinical Significance of Cholesterol in Bile and Blood Serum; Equilibrium of Cholesterol and Cholesterol Ester in Disturbed Liver Function. *Arch. f. exper. Path. and Pharmacol.*, 115:221-231, 1926.
  81. Stroebe, F.: Cholesterinemie bei Lebereirrhose und hepatocellulärer Ikterus. *Klin. Wochenschr.*, 11:636-639, April, 1932.
  82. Stoesser, A. V.: Study of Cholesterol Fractions in Acute Infection of Infants with and Without Eczema. *Proc. Soc. Exper. Biol. and Med.*, 34:10-11, Feb., 1936.
  83. Thannhauser, S. J. and Sehaver, H.: Ueber die Beziehungen des gleichgewichtes cholesterin und cholesterinester in Blut und Serum zur Leberfunktion. *Lip. Wochenschr.*, 5:252-253, Feb., 1926.
  84. Tumen, H. and Boekus, H. L.: Clinical Significance of Serum Proteins in Hepatic Disease Compared with Other Liver Function Tests. *Am. J. Med. Sci.*, 193:788-800.
  85. Turner, K. B. and Stiener, A.: A Long Term Study of the Variations of Serum Cholesterol in Man. *J. Clin. Invest.*, 18:45-49, Jan., 1939.
  86. Weir, J. F.: The Diagnosis of Jaundice, Value of Clinical and Laboratory Data. *Am. J. Surg.*, 15:491-503, March, 1932.
  87. Wendt, H.: Über das Verhalten der Cholesterinester in Bluteserum Leberkranker. *Klin. Wochenschr.*, 8:1215-1218, June, 1929.
  88. Weston, P. G.: Colorimetric Methods for Determining Serum Cholesterol. *J. Biol. Chem.*, 28:383-387, Jan., 1917.
  89. Whipple, G. H.: Protein Production and Exchange in the Body Including Hemoglobin, Plasma Protein and Cell Protein, 196:609-621, Nov., 1938.
  90. White, F. W., Deutsche, E. and Maddock, S.: The Comparative Value of Serial Hippuric Acid Excretion, Total Cholesterol, Cholesterol Ester and Phospholipid Tests in Diseases of the Liver. I. The Results of the Tests. *Am. J. Dig. Dis.*, 5:603, Nov., 1939.
  91. Ynsizumi, Z.: Clinical Significance of Plasma Lipoid Content and Cholesterol Ester. *Tokyo J. Exper. Med.*, 33:165-180, May, 1935.
  92. Ynsuda, M.: On Lieberman-Burchard Reaction of Bound Cholesterol. *J. Biochem. (Japan)*, 24:443-445, Nov., 1936.

## A Comparative Evaluation of the Newer Liver Function Tests \* †

(Comparison of the Intravenous Hippuric Acid Test, the Cephalin-Cholesterol Flocculation Test, the Colloidal Gold Test and a Serial Bromsulphthalein Test With the Oral Hippuric Acid Test and the Rosenthal Bromsulphthalein Test)

By

JOHN G. MATEER, M.D., JAMES I. BALTZ, M.D., DONALD F. MARION, M.D.

and

ROBERT A. HOLLANDS, M.D.

with the assistance of

ELIZABETH M. YAGLE, Ph.D.

DETROIT, MICHIGAN

### INTRODUCTION

IN view of the numerous functions of the liver, and the known dissociation of the results of different liver function tests, the importance of performing several hepatic function tests for any adequate evaluation of liver function is recognized. In this connection, it is important to determine whether the newer tests, devised during the past three years, are preferable to those in common use. Are the newer tests more sensitive than the older tests, and at the same time reliable? The purpose of this communication is to answer these questions.

A comparative statistical study has been conducted to determine the relative sensitivity and reliability of Quick's intravenous hippuric acid test, Hanger's cephalin-cholesterol flocculation test, Gray's colloidal gold test, and a modification of Macdonald's serial bromsulphthalein test, in relation to each other, and to the two older tests, viz., the oral hippuric acid test and the Rosenthal bromsulphthalein test.

In order to determine whether the newer tests were more sensitive, a majority per cent of cases with relatively slight or moderate degrees of known hepatic disease, or with suspected liver impairment, was in-

cluded in the clinical material utilized. At the same time, the clinical material included also a wide variety of types and degrees of liver impairment. A sufficient number of cases with advanced liver disease were studied.

To evaluate the reliability of the newer tests, and to determine the possibility of obtaining false positive results in their use, it was essential to conduct careful control studies upon an adequate group of normal individuals, using each of the four newer tests.

### LITERATURE

#### I. Rosenthal Bromsulphthalein Test

In 1924 Rosenthal and White (1) studied the physiological behavior of various chlorine, bromine and iodine phthalein dyes. These dyes, when introduced into the blood stream, were removed by the liver and excreted into the bile. Bromsulphthalein was found to be the most suitable of these dyes for use as a test of liver function. They found this dye to be non-toxic in the small doses adequate for a test of liver function.

In 1925 the same workers (2) reported the results of the clinical application of the bromsulphthalein test for hepatic function, and described their technique in detail. They advised the intravenous injection of 2 mg. of dye per kilo body weight. From the vein of the opposite arm 4 cc. of blood were withdrawn in 5

\*Read before the Forty-Fourth Annual Meeting of the American Gastro-Enterological Association at Atlantic City, N. J., May 5, 1941.

†From the Gastro-Intestinal Division of the Medical Department, Henry Ford Hospital.

and in 30 minutes. The amount of dye remaining in the blood serum was estimated by colorimetric comparison with a series of standards. Rosenthal's main criterion for a positive test was the retention of any dye in the 30 minute specimen of blood serum.

Rosenthal's test has been in common use since 1925. When positive, this test affords reliable evidence of impaired liver function. The criticism of the test is that it does not detect frequently enough impairment of slight and moderate degrees. In other words, the test lacks sensitivity.

## II. Serial Bromsulphthalein Test

In 1938 Macdonald (3) reported in the Journal of the Canadian Medical Association observations upon the disappearance time of bromsulphthalein from the blood. In 25 *normal* control cases, from which blood specimens were obtained every 2 minutes for a 30 minute period, by a method requiring only a single venapuncture, Macdonald demonstrated that in *every* case not more than 10% of the dye remained in the 14 minute blood specimen. In 22 of the 25 normal cases there was no trace of the dye remaining in 18 minutes. He concluded that the general practice of considering 30 minutes as the normal clearance time constituted a *longer* period than indicated, when 2 mg. of bromsulphthalein per kilo body weight has been injected. (This dose recommended by Rosenthal has been the dose most commonly employed). Macdonald emphasized that an abnormal liver, with its remaining reserve, may perform the same amount of work as a normal liver, if allowed sufficient time. He noted that a *normal* liver should be able to perform a stipulated task *more rapidly* than an impaired organ. He reasoned, therefore, that the *rate* of removal of the dye *during* the 30 minute period should be determined by withdrawing blood frequently during this period, and not simply by relying on a 5 and 30 minute determination. Macdonald reported a small but interesting group of cases with liver damage demonstrable with his *serial* bromsulphthalein method, but not demonstrated by the Rosenthal method.

In 1939 Macdonald (4) reported another group of cases studied by the *serial* bromsulphthalein method. These cases confirmed further the validity of his *serial* method. In this second communication he suggested two further modifications in the method, viz., (1) that a blood specimen be obtained every 5 minutes for 35 minutes, (omitting the first five minute specimen), instead of every 2 minutes for 30 minutes; and (2) that the amount of dye given be increased from 2 mg. to 5 mg. per kilo, in order to furnish a more optimum load of work with which to test the hepatic reserve.

## III. Oral Hippuric Acid Test

In 1936 A. J. Quick (5) emphasized the clinical value of his oral hippuric acid test as a liver function test. In numerous *previous* communications, dating back as early as 1926, Quick published various reports, dealing with the conjugation of benzoic acid and amino-acetic acid to form hippuric acid, with emphasis upon his simple gravimetric method for determination of the amount of hippuric acid excreted in the urine.

The details of the procedure for Quick's oral hippuric acid test, outlined previously (6), were outlined again in the above publication (5). After giving 6 grams of sodium benzoate orally, Quick advised collecting separate complete hourly urine specimens for four hours. The hourly output of hippuric acid in

terms of benzoic acid was determined, and these figures were added, to determine the *total* four hour output. Quick demonstrated that the *normal* adult excreted about 3 gm. of benzoic acid as hippuric acid in four hours; and this figure was adopted as the normal standard.

Quick (5) reported that a decreased output of hippuric acid occurred in cases of catarrhal jaundice and various forms of acute hepatitis, and usually in cases of metastatic carcinoma of the liver and in hepatic cirrhosis. The hippuric acid output *usually* was normal in cases of cholecystitis and cholelithiasis.

In 1936 Snell and Plunkett (7) reported 38 cases of hepatic disease of various types studied by the oral hippuric acid method. Snell used Quick's method except that Snell conducted a single quantitative gravimetric hippuric acid determination upon the total four hour urinary output, obtained by combining the four hourly specimens, instead of making a separate determination upon each of the hourly specimens, and then adding these figures to obtain the total four hour output. Snell and others have emphasized that low hippuric acid values cannot be used as a criterion of impaired liver function if (1) there is sufficiently marked *renal* impairment to cause elevation of blood urea, or, (2) if the patient is dehydrated to a point where water elimination and urinary volume are reduced, or, (3) if gastric retention exists.

Another occasional condition which may render results unreliable is the presence of sufficient prostatic hypertrophy to interfere with normal emptying of the bladder.

Snell concluded from his study of patients with various types of liver damage that the oral hippuric acid test has peculiar merit in that it usually affords reliable and helpful information about impaired liver function in *jaundiced* patients. In the "surgical" types of jaundice he found the test especially helpful in estimating the *degree* of liver damage and the *operability* of the patient. He stated that, if the four hour hippuric acid elimination (expressed in terms of benzoic acid) is reduced to 1.5 gm., or less, severe hepatic damage exists, and surgical procedures will involve a considerable risk. Snell further stated that in the *non-icteric* patient also the hippuric acid test "appears to give accurate information."

In 1938 Boyce and McPetridge (8) also reported a series of cases of different types of liver damage studied by a slight modification of the oral hippuric acid method of Quick. These authors, after following Quick's method exactly for some time, simplified the method beyond Snell's modification, by collecting only one urine specimen at the end of the four hour period, instead of collecting hourly specimens. Like Snell, they conducted only one gravimetric determination upon the total four hour output. After conducting a series of comparative tests, Boyce and McPetridge concluded that this *simplified* method is "equally accurate" to Quick's original method. They emphasized the importance of *repeating* the test if the first reading is low. These authors used the test during the preparation of patients for operation, and also during the post-operative course. They found the test useful in determining the proper course of preoperative and post-operative procedure. The test demonstrated the degree of improvement in hepatic function occurring

after high carbohydrate intake before operation; and it also revealed the drop in liver function occurring the first day or two after operation.

#### IV. Intravenous Hippuric Acid Test

In 1938 Quick (9) and his associates reported a method for conducting an *intravenous* hippuric acid liver function test. They advised the intravenous injection of 1.77 gm. of sodium benzoate (equivalent to 1.5 gm. benzoic acid) dissolved in 20 cc. of distilled water. The subject was asked to void just before the test started, and a complete urine specimen was collected exactly one hour after the completion of the injection. Approximately 5 minutes were allowed for the injection. The hippuric acid was determined by Quick's simple gravimetric method (6). Quick reported that normal adults excreted from .70 to .95 gm. of benzoic acid as hippuric acid during this 1 hour period. He suggested that this *intravenous* test could be used as an alternative to the *oral* method.

In May, 1939, Lipschutz (10) reported an *intravenous* hippuric acid test which involved the injection of 2 gm. of sodium benzoate, followed by the collection of 1 hour and 2 hour urine specimens. He then added the two hippuric acid outputs, expressed in terms of benzoic acid, and determined the *per cent* of the 2 gms. of sodium benzoate injected which this total 2 hour excretion represented. In comparing the *per cent* of benzoic acid excreted by Quick's oral method and his intravenous method, Lipschutz reported that the *per cent* of the introduced benzoic acid which was excreted was a little higher with his intravenous method than with Quick's oral method, but that there was a close parallelism between the results obtained from the two methods.

In December, 1939, Quick (11) published a second article upon the *intravenous* modification of the hippuric acid test for liver function. Quick emphasized that Lipschutz' method was open to two criticisms.

In the first place Lipschutz' results depend upon the calculation of the *per cent* of administered benzoic acid which is excreted as hippuric acid, whereas Quick's intravenous test simply measures the *rate* at which any particular liver can synthesize hippuric acid. Quick had previously demonstrated that the maximum amount of hippuric acid which can be synthesized by any liver is limited, practically constant, and independent of the exact amount of sodium benzoate injected—*provided* one gives benzoic acid in *excess* of the liver's capacity to synthesize it all with glycine within a fixed period of time.

In the second place, on a group of individuals with a *normal* liver reserve, who received 1.77 gms. of sodium benzoate intravenously, Quick showed that a much smaller amount of benzoic acid was excreted as hippuric acid during the second hour than during the first hour. In other words, only the *first* hour excretion measures the *maximum* capacity of the normal liver to synthesize hippuric acid. Quick noted that a liver with *impaired* function, which excretes only 70% of the minimum normal output of .7 gm. in 1 hour, will excrete approximately the *same* amount, viz., .5 gm., the *second* hour. This *total* excretion of 1.0 gm. for 2 hours would fall, therefore, within the *normal* range of excretion, according to Lipschutz' 2 hour method. Obviously, therefore, the 1 hour intravenous method of Quick is a *more sensitive* test in detecting impair-

ment of liver function than the 2 hour test of Lipschutz.

In this more recent article of Quick's (11), he also reported that the accuracy of the quantitative determination of hippuric acid in the urine can be increased further by adding ammonium sulphate before precipitating the hippuric acid.

#### V. Cephalin-Cholesterol Flocculation Test

In 1938 Hanger (12) reported a simple test by which disturbances in the liver parenchyma could be detected by noting the capacity of the blood serum of these cases to flocculate a colloidal suspension of a cephalin-cholesterol emulsion. He stated that the positive readings are made in terms of plus signs, a ++++ reaction indicating a complete precipitation of the lipid emulsion, with no remaining turbidity of the supernatant fluid. Hanger reported that over 900 examinations were made upon the sera of normal individuals, or of patients selected at random from the medical wards. Hanger stated that "flocculation was consistently absent in all *normal* cases, but occurred in most instances when active disease of the liver parenchyma was present." This author further stated that "all cases of catarrhal jaundice, examined at the height of the attack, gave a positive reaction which gradually became weaker and finally negative as clinical improvement took place. Cases of obstructive jaundice (except those of long standing) gave a negative reaction." In cases of cirrhosis the degree of flocculation paralleled the severity of the process as a rule, "and was negative in those instances in which residual scarring was apparently the sole lesion." Hanger emphasized that this flocculation test "does not parallel the Wassermann reaction, the albumin-globulin ratio, serum bilirubin, blood cholesterol, serum phosphatase, the Takata-Ara reaction, the formol-gel test or erythrocyte sedimentation rate."

In 1939 Hanger (13) reported a further group of cases with different types of liver damage, studied by the cephalin-cholesterol flocculation test. In general, this further study confirmed his earlier observations. In this later publication the author emphasized especially the value of this test in differentiating hepatogenous from obstructive jaundice, and also in following the course of hepatogenous jaundice.

In 25 cases of *obstructive* jaundice studied, 11 cases had been jaundiced from 1 month to 1 year. There were no cases showing more than a one + reaction; and only 4 out of the total 25 cases showed either a + or only reaction. In other words, the test usually remained negative even in long-standing obstruction.

In 38 cases of hepatic jaundice, e.g., acute hepatitis (catarrhal jaundice) and cirrhosis, 35 cases gave a positive test.

In the prognosis of acute hepatitis, the progressive decrease and final disappearance of an original ++++ test, before the jaundice had disappeared, indicated an excellent prognosis. On the other hand, Hanger noted that the *continued* persistence of a ++++ test, irrespective of a decrease in the degree of jaundice, indicated progressive liver degeneration and often an unfavorable prognosis.

This author also observed that the above flocculation test was more sensitive than the liver function tests in common use. As to the mechanism involved in this flocculation test, final information is not yet available. Hanger thinks it probable, however, that flocculation



"depends upon the capacity of an altered globulin constituent of the serum to become affixed to the colloidal elements of the emulsion."

In his second publication (13) Hanger also reported that in all the normal control cases studied, he had found no significant flocculation reaction except in one apparently healthy medical student. In this same publication (13) Hanger also reported in detail the method of preparing his emulsion, the technique of conducting the test, and the method of interpretation.

Only two months ago, Pohle and Stewart (14) reported the cephalin-cholesterol flocculation reaction with sera from patients with a variety of hepatic disorders.

These authors reported that 284 normal individuals were studied, and in no instance did significant flocculation occur. The test was performed upon the sera of 455 patients with a variety of extra-hepatic diseases, but with no clinical evidence of liver disease. A positive reaction was obtained in 15 of these cases (3.3%).

Pohle and Stewart studied 141 patients with hepatic or biliary tract disease, including acute toxic hepatitis, cirrhosis of the liver, obstructive jaundice and focal lesions of the liver. They obtained a positive cephalin flocculation test in a very high per cent of these cases. They concluded that this test is a more sensitive index of hepatic disease "than many of the functional studies." On the other hand, unlike Hanger, they did not find the cephalin flocculation test a reliable guide for the differentiation of obstructive from hepatogenous jaundice. 78% of their *obstructive* jaundice cases gave some degree of a positive flocculation test.

In this connection, it is only fair to state that in the majority of Pohle and Stewart's cases with obstructive jaundice the jaundice had *persisted* for one month or longer when the test was conducted. On the other hand, in a majority of Hanger's cases of obstructive jaundice the cephalin test was conducted *less* than a month after the onset of jaundice; and in a number of his cases the icterus had been present less than *two* weeks. Hanger's cases of acute hepatitis, as a group, were studied even *earlier* in the course of the icterus. This probably explains, at least in part, why Hanger found the cephalin test more helpful in differentiating obstructive and hepatic jaundice than did Pohle and Stewart.

#### VI. Colloidal Gold Test

In 1940 Gray (15) reported an hepatic function test based upon the colloidal gold reaction of the blood serum in cases of liver disease. The description of the *method* of conducting this test is rather brief in Gray's published article (15). It is suggested that any worker in this field contemplating the use of the colloidal gold test should *first* obtain from Gray his unpublished, *detailed*, mimeographed directions for preparation of the colloidal gold solution, for its subsequent standardization and acidification, and for the conduct of the test. Space does not permit the inclusion here of those detailed directions.

Briefly, however, the main steps in this colloidal gold method are as follows: (1) Gray advises the use of Klaas' modification of Patterson's method in preparing the gold solution. (2) Whenever a new supply of colloidal gold solution is made, its acid requirement must be determined by standardizing it against a known positive serum (obtained from a patient known

to have liver disease), and against a known negative or normal serum. (The *sensitivity* of the gold reaction may be increased or decreased by increasing or decreasing the amount of hydrochloric acid added to the gold solution). Various amounts of fiftieth normal HCl are added to 50 cc. volumes of colloidal gold solution. Each of these acidified preparations is tested against the known positive and negative serum, by the detailed method shown in the table included in Gray's mimeographed, detailed directions. The ideal acid requirement is the amount of acid giving the best combination of the strongest positive test (paretic curve) with the "known positive" serum, and the best negative test with the normal control serum. In order to be sure that this amount of acid is actually the ideal amount to add, Gray advises in his *mimeographed* directions that 10-20 normal sera should then be tested, (using the above ratio of acid to gold solution), to determine whether any false positive reactions occur. He states that "if false positives occur, less acid should be used." In other words, the amount of acid added should be gradually reduced until no false positive tests occur with the 10-20 normal sera. The ideal ratio of acid, (determined by this rather laborious method of standardization of the gold solution), is added then each day, just before conducting the tests, to the amount of gold solution needed. (3) Three tubes are needed for each test; and a specific increased dilution of the patient's serum with salt solution is provided for each successive tube. Five cc. of colloidal gold solution, (properly acidified), are added then to each tube. The tubes are read in 12-24 hours. (4) Any reading starting with a 5, indicating complete precipitation of the gold, e.g. 553, 543, or 522, constitutes a *positive* test. Any reading which starts with a number below 5, e.g. 432, 321, or 221, is regarded as a *negative* result.

Upon the basis of more recent and extended experience with the colloidal gold method, Gray has made one important change from his published technique. In his published article (15) he states that "standardization need be done only once for each supply of colloidal gold prepared, since several liters may be kept for as long as several months without changing the acid requirement." In a recent personal communication of March 12, 1941, to the authors, Gray revises the above statement as follows, viz., "we check the standardization and acid requirement of our colloidal solution every two weeks. If this is not done, difficulties may arise because the pH of the gold changes as time goes on, and thus the acid requirement usually goes up." He also states that "we have found that at the end of six weeks the gold changes so much that a new supply of gold should be prepared."

Gray studied the colloidal gold reaction of the blood serum in a total series of 96 cases of hepatic disease. The gold reaction was positive in all 46 cases of hepatic cirrhosis studied. The impression was gained from a study of Gray's tables that the majority of these cases represented an advanced stage of hepatic cirrhosis. In Gray's study the gold reaction was positive in 13 of 14 cases of acute parenchymatous hepatic involvement, in 19 of 25 cases of neoplastic involvement of the liver, and in each one of 11 cases of miscellaneous hepatic disease.

Gray emphasized that the colloidal gold reaction was considerably more sensitive than the Takata-Ara reaction, the plasma cholesterol reading, quantitative variations in the plasma albumin and globulin, and the other liver function tests employed in his study.

He stated that the mechanism of the colloidal gold reaction is unknown. Furthermore, he noted that it does not depend primarily upon a quantitative increase of the globulin, nor upon an inversion of the albumin globulin ratio, but "it may depend on a *qualitative* rather than on a quantitative variation in the plasma globulin, and the euglobulin may be an important factor in the reaction."

#### METHODS USED

I. Rosenthal's bromsulphthalein method, as originally reported (2), and as summarized above, was employed in this study. 2 mg. of dye per kilo of body weight were administered; and blood specimens were withdrawn at 5 and 30 minutes after injection of the dye.

II. The *serial* bromsulphthalein method employed was a modification of the serial dye method described by Macdonald in his first publication (3). The method employed in the following study consisted of injecting 2 mg. of bromsulphthalein dye per kilo body weight, the same dose as employed by Rosenthal (2) and Macdonald (3). A blood specimen was withdrawn from the opposite arm every 5 minutes for a 30 minute period, instead of every 2 minutes for 30 minutes, as suggested by Macdonald in his first publication (3). A *single* venapuncture was done for the withdrawal of the six blood specimens of 4 cc. each. The needle, with a three way stop cock attached, was connected with a gravity apparatus containing normal saline solution. Between successive withdrawals of blood, the salt solution was allowed to run *slowly* into the vein to prevent clotting. (Two of these serial tests were conducted at the same time by a specially trained nurse, sitting between the two reclining patients in the technique room. In collecting the blood specimens there was ample time for the nurse to alternate from one patient to the other, each blood specimen being collected at exactly the right time). The per cent of dye remaining in each blood serum specimen was determined by the colorimetric method used in the Rosenthal test.

It was not necessary to conduct the Rosenthal test as a test *separate* from the *serial* dye test. Since the same dose of dye, viz., 2 mg. per kilo, was employed for both tests, the 5 minute and 30 minute determinations of the serial bromsulphthalein test *constituted* the readings of the Rosenthal test.

(The authors plan shortly to proceed a step further, and compare the *sensitivity* of the above serial dye method with the serial bromsulphthalein method advocated by Macdonald in his *second* publication (4), viz., injecting 5 mg. of dye per kilo, instead of 2 mg. per kilo. Macdonald has demonstrated evidence to suggest that the 5 mg. dose affords a more ideal dose with which to test the hepatic reserve, since this dose requires the performance of the maximum amount of work which the normal liver can perform in a short time).

III. The *oral* hippuric acid method used was Boyce's modification (8) of Quick's oral method (6). This simplification consisted of collecting a *single* urine specimen 4 hours after ingestion of the sodium

benzoate, and then performing a single quantitative hippuric acid determination upon this specimen, using Quick's gravimetric method.

IV. Quick's *intravenous* hippuric acid method was employed, essentially *unchanged*, as published 3 years ago (9), and as summarized above. The authors agree with Quick that this test should be a *one* hour, and not a two hour, estimation of liver function. The only slight change in the method employed by the authors consisted of taking 8 minutes, instead of 5, for the injection of the 20 cc. of sodium benzoate solution. This slower injection tends to minimize or prevent the occasional symptoms of *transient* faintness, sweating, slight epigastric distress, or flushing of the face. Any symptom which may occur tends to disappear if the rate of injection is retarded further, or almost stopped for a moment. Counting the repeat progress tests, more than 250 of these intravenous injections of sodium benzoate solution have been conducted. No marked or serious reaction of any sort has been observed in any instance. (It is important, of course, that the sodium benzoate solution should be properly prepared for intravenous use\*).

V. Hanger's cephalin-cholesterol flocculation method was employed, unchanged, as published 3 years ago (12), and again 2 years ago (13), and as summarized above.

VI. Gray's colloidal gold method was employed, as published one year ago (15) and summarized above. However, Gray's suggestion, in his unpublished mimeographed directions, to run 10-20 normal control sera when standardizing each new supply of gold was *not* followed. When evaluating the method, 40 normal control sera were tested. However, while using this method as a routine laboratory procedure, it did not seem practical to expend the time and effort required to collect 10-20 normal sera, and test them for false positive results, every time it was necessary to standardize a new gold solution, or restandardize a supply on hand. This seemed especially true since Gray has found it essential to *restandardize* the stock supply of gold solution every *two* weeks, as noted above. The work involved, to render the test reliable, is too great for a routine laboratory procedure.

In this study, Gray's initial method of standardization of the gold solution was followed, using the serum of a normal individual and that of a patient with definitely known liver disease. For subsequent tests the amount of acid was added to the gold solution which yielded the best *combination* of the best negative reading with the normal serum and the best positive reading with the "positive serum."

The serum of a healthy young individual, who had been found normal with the other newer liver function tests, was used as the "normal control" serum for the standardization of the gold solution used for the study of the 40 normal control individuals. And the serum of this *same* normal individual was used, along with a "known positive" serum in standardizing *subsequent* new supplies of gold solution used in testing patients. In this way it was felt that any slight error in sensitivity, or deviation from the ideal acid requirement, would be *constant* in the group of patients tested, and the *same* as found in the group of 40 normal control

\*20 cc. ampoules of sodium benzoate solution for this test have been obtained from Hynson, Westcott and Dunning, Baltimore.



cases. In other words, it seemed reasonably accurate under the above conditions to assume that there would be approximately the same small *per cent* of false positive tests in the group of patients, as found in the normal control group. If desired, the small *per cent* of false positive tests found in the normal control group could be subtracted from the total number of positive tests in the groups of patients. Actually this small subtraction was not made in the statistical tables.

*Titration of colloidal gold solution for 40 normal control sera*

| cc. Fiftieth Normal HCl to 50 cc. Gold S. | Normal Serum | "Known Positive" Serum From Patient with Liver Disease |
|---|--------------|--|
| 0.8 cc.                                   | 221          | 432  |
| 0.9                                       | 321          | 432  |
| 1.0                                       | 321          | 432  |
| 1.1                                       | 321          | 542  |
| 1.2                                       | 321          | 543  |
| 1.3                                       | 431          | 543  |
| 1.4                                       | 431          | 543  |
| 1.5                                       | 431          | 543  |

1.2 cc. HCl was chosen as the optimum amount of acid to add.

One limitation of the colloidal gold test is the *variation* in the readings upon sera of different *normal* individuals, using the same supply of gold solution and the same acidification. For example, in Table I, the colloidal gold readings upon 40 normal subjects varied from 321 to 543.

Whether *false positive* tests are, or are not, obtained, with gold solution standardized by titrating a "normal serum" against a "positive serum," will depend partly, therefore, upon whether an *ideal* normal serum *happened* to be selected for use. In restandardization of the gold solution, the use of serum from the same normal individual tends to render any *deviation* from the ideal sensitivity *relatively constant*. The use of the same "known positive" serum is often not possible. In a few instances, even serum from the same normal subject, when tested again a couple of days later, with the same acidification of the same supply of gold solution, gave a *different* reading when tested the second time, e.g. in one normal individual changing from 543 to 432.

### NORMAL CONTROL STUDIES

A group of forty healthy young adults, consisting mainly of young physicians, but including a few nurses, served as a normal control group. A careful gastro-intestinal history, (past and present), was obtained, and no one was included who had had catarrhal jaundice or other previous gastro-intestinal condition which reasonably could have left any residual liver impairment. Nor was anyone included who had had any recent acute infection, which might impair liver function temporarily.

Only the four *newer* hepatic function tests were conducted upon the normal control group. Control studies seemed unnecessary in the case of the two older tests.

In Table I the results of these four tests upon the

group of 40 normal control individuals are summarized. These results are compared with the results of normal control studies conducted by the author of each of these tests.

#### I. Intravenous Hippuric Acid Test

The lowest reading observed with the intravenous hippuric acid test upon this normal group was .70 gm., occurring in Case 10. Only three of the 40 cases exceeded a reading of 1.15 gm. These results check closely with Quick's results upon normal individuals. He also reported .70 gm. to be the low limit of normal; and his major variation of readings was from .70 to .95 gm. The fact that in 15 of our 40 normal individuals the reading was above .95 gm. is probably due partly to the fact that we allowed 8 minutes for intravenous injection of the sodium benzoate, instead of the 5 minutes suggested by Quick. This permitted 3 extra minutes for hippuric acid synthesis to occur. Furthermore, a few of our controls were quite large individuals. Quick has emphasized that the size of the subject does exert a slight influence upon the amount of hippuric acid synthesized. In this con-

TABLE I  
Normal controls — Hepatic function studies  
(Healthy young doctors and nurses with negative history)

| Controls No. | I.V. Hippuric Acid Test | Serial Bromsulphthalein Test |                  | Cephalin-Cholesterol Flocculation Test | Colloidal Gold Test |
|--------------|-------------------------|------------------------------|------------------|--|---------------------|
|              |                         | Minutes                      | 5-10-15-20-25-30 |  |                     |
| 1            | 1.05                    | 30                           | 5 Tr 0 0 0       | 0                                      | 332                 |
| 2            | 1.05                    | 40                           | 15 5 0 0 0       | 0                                      | 432                 |
| 3            | .94                     | 20                           | 0 0 0 0 0        | 0                                      | 332                 |
| 4            | .75                     | 30                           | 5 0 0 0 0        | 0                                      | 431                 |
| 5            | .88                     | 40                           | 7 Tr 0 0 0       | 0                                      | 532                 |
| 6            | .96                     | 27                           | 7 0 0 0 0        | 0                                      | 432                 |
| 7            | 1.40                    | 55                           | 5 0 0 0 0        | 0                                      | 432                 |
| 8            | .97                     | 35                           | 7 Tr 0 0 0       | +                                      | 331                 |
| 9            | .89                     | 60                           | 20 5 0 0 0       | 0                                      | 332                 |
| 10           | .70                     | 60                           | 20 5 0 0 0       | 0                                      | 321                 |
| 11           | 1.15                    | 55                           | 25 10 0 0 0      | 0                                      | 532                 |
| 12           | .89                     | 30                           | 7 3 0 0 0        | 0                                      | 321                 |
| 13           | .91                     | 50                           | 3 Tr 0 0 0       | 0                                      | 321                 |
| 14           | 1.18                    | 45                           | 20 Tr 0 0 0      | 0                                      | 432                 |
| 15           | 1.02                    | 35                           | 15 0 0 0 0       | 0                                      | 321                 |
| 16           | .95                     | 27                           | 5 0 0 0 0        | +                                      | 332                 |
| 17           | .82                     | 40                           | 12 5 0 0 0       | 0                                      | 321                 |
| 18           | 1.11                    | 35                           | 5 0 0 0 0        | 0                                      | 321                 |
| 19           | .78                     | 50                           | 15 0 0 0 0       | 0                                      | 432                 |
| 20           | .80                     | 25                           | 10 5 0 0 0       | 0                                      | 432                 |
| 21           | .74                     | 50                           | 20 5 0 0 0       | 0                                      | 432                 |
| 22           | .72                     | 25                           | 5 0 0 0 0        | 0                                      | 332                 |
| 23           | .90                     | 35                           | 10 5 0 0 0       | +                                      | 332                 |
| 24           | 1.04                    | 27                           | 10 0 0 0 0       | 0                                      | 432                 |
| 25           | 1.00                    | 40                           | 10 Tr 0 0 0      | 0                                      | 432                 |
| 26           | 1.15                    | 30                           | 5 0 0 0 0        | 0                                      | 432                 |
| 27           | 1.32                    | 25                           | 5 0 0 0 0        | 0                                      | 431                 |
| 28           | .91                     | 30                           | 10 0 0 0 0       | 0                                      | 543                 |
| 29           | .94                     | 30                           | 5 0 0 0 0        | 0                                      | 332                 |
| 30           | 1.01                    | 35                           | 10 0 0 0 0       | 0                                      | 432                 |
| 31           | .96                     | 27                           | 10 0 0 0 0       | 0                                      | 432                 |
| 32           | 1.11                    | 30                           | 7 0 0 0 0        | +                                      | 321                 |
| 33           | .84                     | 40                           | 15 Tr 0 0 0      | 0                                      | 432                 |
| 34           | .80                     | 30                           | 8 Tr 0 0 0       | 0                                      | 321                 |
| 35           | .82                     | 30                           | 5 0 0 0 0        | 0                                      | 322                 |
| 36           | .83                     | 45                           | 20 0 0 0 0       | +                                      | 543                 |
| 37           | .83                     | 25                           | 10 0 0 0 0       | 0                                      | 332                 |
| 38           | .74                     | 45                           | 15 5 0 0 0       | 0                                      | 432                 |
| 39           | .88                     | 35                           | 5 0 0 0 0        | 0                                      | 432                 |
| 40           | .93                     | 25                           | 5 0 0 0 0        | 0                                      | 321                 |

†Tr indicates a trace of dye.  
\*+ results of cephalin test are only faintly positive in the control group, on the basis of a +, ++, +++, and ++++ system.  
†The four colloidal gold readings starting with a 5 indicate complete precipitation of the gold in the first tube, and represent positive tests.

nection, Case 10 in the control group with the lowest excretion (.70 gm.) was a nurse weighing less than 115 lbs. The other readings below .80 gm. also occurred in the *smaller* members of the group.

## II. Serial Bromsulphthalein Test

In reviewing the *serial* bromsulphthalein readings, it will be noted that if 20 minutes be regarded as the maximum time for complete clearance of the dye from the blood stream, all 40 normal controls yielded a negative test, with no "false positives." It is also noted that in 55% of this normal group the dye had disappeared in 15 minutes. Macdonald found, when using the 2 mg. per kilo dose, that in almost all of his normal subjects the dye had disappeared in 18 minutes. The authors of this paper have regarded 20 minutes, therefore, as the conservative *normal* clearance time. If any dye remained in the 20 or 25 minute blood specimens, the test was regarded as *positive*—though it may have cleared in 30 minutes, the normal clearance time previously advocated by Rosenthal for a 2 mg. per kilo dose.

## III. Cephalin-Cholesterol Flocculation Test

Upon analysis of the results of the cephalin-cholesterol flocculation test upon the normal group, 12½%, or 5 of the 40 subjects exhibited faintly *one +* false positive readings. These appeared, not at the first 24 hour reading, but were apparent at the 48 hour reading. There were *no ++, +++, or ++++* readings in any of the 40 normal subjects. It was possible, therefore, in the subsequent tests upon patients, to make this test *reliable* by considering the *one +* results as normal. In the total group of cases having this test, this necessitated eliminating exactly 25% of the *total positive* cephalin tests. This adjustment may have resulted in excluding *some* bona fide faintly positive tests. For it does not follow necessarily, because there were 12½% of false faintly positive *one +* tests in the *normal* group, that *all* of the 25% of *one +*, or faintly positive, results with *patients* were *false* positive results. However, the first consideration is to make the test reliable, even if *some* of the sensitivity is sacrificed. Even with this restriction the cephalin test subsequently proved to be extremely sensitive.

In a recent personal communication from Hanger, under date of March 26, 1941, he writes as follows, viz.: "In answer to your question regarding the significance of 1+ reactions in normal individuals, I can say that it depends entirely upon the sensitiveness of your cephalin preparation. We have found if the cephalin is put into ether soon after preparing, before it has turned dark and gummy, that a weakly positive reaction is not unusual in normal individuals, particularly if the room is kept at low temperature. In the last year, however, since we have employed only a cephalin which has been ripened in air and sunlight for about six weeks, a positive reaction is practically unknown." (Hanger here obviously refers to *false* positive reactions). Hanger then continues as follows: "If you use a relatively insensitive cephalin, as I have suggested, I feel that a 1+ reaction is probably of clinical significance. The interpretation of your studies should be based upon the sensitivity of the emulsion used."

In the studies reported in this paper, the authors have used the more sensitive, *unripened* cephalin preparation, as advised in Hanger's paper (13) published in 1939. The improved, less sensitive,

*ripened* cephalin, *recently* recommended by Hanger, has the obvious advantage of rendering the faintly positive 1+ results reliable in indicating some degree of liver impairment.

## IV. Colloidal Gold Test

In reviewing the results of the colloidal gold test, in the 40 normal subjects, 10%, or 4 out of the 40 normal individuals, yielded false positive readings. Since each of these readings of the false positive tests started with a 5, indicating *complete* precipitation of the gold in the first tube, these results, (*unlike* the false positive tests with the cephalin test), cannot be regarded as only *faintly* positive. Nor is there any *simple* way to *eliminate* the false positive readings in patients. For reasons already discussed, the only way in which false positive results with the colloidal gold test could have been avoided would have been to conduct 10-20 normal control studies every 2 weeks when restandardizing the gold solution. (On this basis, it would have been necessary to decrease the amount of acid added to a point where no false positive results occurred). This is a *very* laborious procedure for a routine laboratory test. It was not followed in this study.

When comparing our results of the colloidal gold test upon patients with those of the other tests performed, it should be kept in mind that the colloidal gold test is a little *more* sensitive than it would be if sufficiently less acid had been added to the gold solution, (in standardizing each new supply), to *avoid any* false positive results.

On the other hand, for reasons stated above, the 1+ false positive *cephalin* tests were *excluded* from our statistics.

## CLINICAL MATERIAL UTILIZED

A sub group of 112 cases with definite *clinical* evidence of liver disease were included in the entire group of 307 cases studied. (See Table II). The 52 cases of hepatic cirrhosis, with *slight* and *moderate* degrees of impaired liver function, and no ascites, all presented varying degrees of demonstrable liver *enlargement*. The exact histological picture of the liver in these 52 cases doubtless varied considerably. In some, fatty infiltration was probably present. Of the 112 cases about half had slight or moderate liver impairment, and the other half were cases with marked liver damage. (See Table II for details).

It became apparent early that the four newer liver function tests were much more sensitive than the older tests in common use. In order to demonstrate this greater sensitivity, it seemed advisable to *include* a large number of cases with presumably only *slight* to *moderate* liver impairment. In view of this consideration, 127 cases with gall stones, but no *direct* clinical evidence of liver impairment, were included. A *miscellaneous* group of 68 cases were also included. Some of these 68 cases presented features suggesting the possibility of associated liver impairment; but a number of them presented conditions not commonly associated with any liver impairment.

## NUMBER OF TESTS CONDUCTED

In Table III is listed the number of tests conducted with each method. A total of 1013 tests were conducted upon 307 patients, or an *average* of approximately three tests per patient. All of this work was

conducted upon *private* patients, and it was not feasible to conduct *all* six tests upon each patient. This necessitated studies upon a larger group of patients in order to obtain adequate comparative data. It also necessitated a comparison of tests by *pairs*. Each test was compared with each of the other five tests.

The evaluation of the intravenous hippuric acid test and the serial bromsulphthalein test was started early in 1939. The additional comparison of the colloidal gold and cephalin tests was not started until after the middle of 1940. This explains the difference in the number of each of the newer tests conducted. There were fewer *oral* hippuric acid tests conducted because,

TABLE II

*Clinical material utilized for liver function studies*

|   | No. Cases Studied |       |       |
|---|-------------------|-------|-------|
|   | J.*               | N.J.† | Total |
| Hepatic Cirrhosis (without ascites—earlier cases)‡  | 13                | 39    | 52    |
| Hepatic Cirrhosis (with ascites—late cases)   | 3                 | 6     | 9     |
| Metastatic Carcinoma of Liver (late cases)  | 23                | 8     | 31    |
| Acute hepatitis (various stages)  | 18                | 2     | 20    |
| (1) Total cases in above groups with definite clinical evidence of liver disease  | 57                | 55    | 112   |
| (2) Cholelithiasis (total cases studied)  | 30                | 97    | 127   |
| (a) Operated cases—studied before operation   | 67                |       |       |
| (b) Operated cases—studied after operation  | 22                |       |       |
| (c) Unoperated cases—probable or definite stones  | 38                |       |       |
|   | 127               |       |       |
| (3) Miscellaneous group (possible liver impairment)<br>(Includes cases of peptic ulcer, thyroid adenoma, chronic irritable colon, myocardial insufficiency and a variety of other conditions—some unrelated to liver) |                   |       | 68    |
| Total cases studied   |                   |       | 307   |

\*J. refers to the presence of some degree of jaundice. This was frequently slight.

†N.J. refers to the absence of any jaundice.

‡All of these cirrhosis cases without ascites presented evidence of hepatic enlargement. This was of variable degree. Two-thirds of these cases presented a marked alcoholic history. Evidence of one type or another of chronic gall tract disease was present in the remaining third of the cases, and also in a number of those cases with an alcoholic history. The exact histological picture of the liver in these 52 cases doubtless varied considerably.

when it was necessary to omit one test, it was elected to omit the oral hippuric acid test rather than one of the four, newer, more sensitive tests. The Rosenthal readings were obtained by utilizing the 5 and 30 minute readings of the serial bromsulphthalein test.

#### COMPARATIVE SENSITIVITY OF FOUR NEWER LIVER FUNCTION TESTS WITH TWO OLDER TESTS, AND WITH EACH OTHER

Under Table IV, fifteen subtables have been constructed. Each subtable compares directly upon identical patients, the sensitivity of one of the six liver function tests with one of the other five tests. Each of the various subtables includes studies upon a group of various types of cases within the total group of 307 cases.

Space permits the publication of only nine of these fifteen subtables, viz., subtables (a), (b), (c), (d), (e), (f), (g), (h) and (i). In comparing these nine subtables, all show the same order of sensitivity of the six tests. In these subtables *direct* comparisons of one test with another upon *identical* cases constitute a more *accurate* index of the relative sensitivity of any two tests than *indirect* comparisons of any two tests with a third test. Indirect comparisons are carried out upon two different groups of cases, presenting varying degrees of liver impairment. The various subtables under Table IV, with their footnotes, are self-explanatory.

In subtable (a), the fact that the intravenous hippuric acid test yielded, upon identical cases, 85% more positive tests than the oral hippuric acid test is not surprising. For the intravenous method tests the maximum amount of work the liver can perform in a short period of time, viz., *one hour*; whereas, the oral method allows *four* hours for the slightly impaired liver to *overtake* the normal liver in the amount of work performed. And yet this *superior* sensitivity of the intravenous method over the oral method has not

TABLE III

*Number of hepatic function tests conducted upon 307 patients\**

(Independent of repeat progress tests)

|                                  |       |
|----------------------------------|-------|
| Oral Hippuric Acid Tests         | 23    |
| Rosenthal Bromsulphthalein Tests | 216   |
| Serial Bromsulphthalein Tests    | 205   |
| I.V. Hippuric Acid Tests         | 210   |
| Cephalin-Cholesterol Tests       | 122   |
| Colloidal Gold Tests             | 170   |
| Total Tests                      | 1011† |

\*These were all *private* patients. It was, therefore, not feasible to conduct all six tests on each patient.

†An average of a little over three tests were conducted on each patient. More patients were studied in order to obtain adequate comparative data.

been *demonstrated* or emphasized up to the present time, to our knowledge. In fact, the *intravenous* method has been used in very few hospitals. We believe it deserves much wider use. It is not only a very sensitive test, but it is a true hepatic function test, testing a synthetic and also a detoxifying function of the liver.

The last four figures in each subtable of Table IV refer to the cases in which both tests were negative. The first of these last four figures refers to cases "with clinical evidence of liver disease." It is the most significant negative figure. The second negative figure, "referring to cases with operative evidence of liver disease," usually referred only to slight scarring of the liver noted at operation. The last two negative figures were often relatively large, but do not discredit the tests, since in the gall stone and miscellaneous groups there was no direct clinical evidence of liver impairment. These last two figures emphasize an essential distinction between evidence of functional impairment and evidence of liver disease.

In subtable (b) of Table IV, it was not surprising that the *serial* bromsulphthalein method, using the same 2 mg. per kilo dose of dye, should have demonstrated 100% more *positive* results than the Rosenthal method. The serial method determines the *rate* of

hepatic work, and the amount of work performed in a shorter time than that allowed by the Rosenthal method.

The findings in subtable (c) of Table IV are of especial interest. Although the intravenous hippuric acid test yielded 54% more positive tests than the serial bromsulphthalein test, the latter test gave a positive result in 13 cases in which the former more

TABLE IV  
*Comparative sensitivity of four newer liver function tests with two older tests, and with each other.*  
*Individual tables*

(a) Comparison\* Intravenous Hippuric Acid and Oral Hippuric Acid Tests Upon All Clinical Groups—Identical Cases

|   | No. Cases |
|---|-----------|
| Both tests done (various types of cases)                  | 68        |
| Both tests positive                                       | 19        |
| Intravenous Hippuric Acid test alone positive†            | 20        |
| Oral Hippuric Acid test alone positive                    | 2         |
| Both tests negative—clinical evidence liver disease       | 5         |
| Both tests negative—operative evidence liver disease      | 3         |
| Both tests negative—gall stones—no evidence liver disease | 10        |
| Both tests negative—Misc. (possible liver impairment)     | 9         |

\*Intravenous Hippuric Acid test yielded positive tests in 85% more cases than the Oral Hippuric Acid test.

†The reason for the greater sensitivity of the intravenous method is obvious.

(b) Comparison\* Serial Bromsulphthalein† and Rosenthal Tests Upon All Clinical Groups—Identical Cases

|   | No. Cases |
|---|-----------|
| Both tests done (various types of cases)                  | 205       |
| Both tests positive                                       | 31        |
| Serial Bromsulphthalein test alone positive               | 31        |
| Rosenthal Test alone positive                             | 0         |
| Both tests negative—clinical evidence liver disease       | 41        |
| Both tests negative—operative evidence liver disease      | 23        |
| Both tests negative—gall stones—no evidence liver disease | 34        |
| Both tests negative—Misc. (possible liver impairment)     | 45        |

\*Serial Bromsulphthalein Test yielded positive tests in 100% more cases than the Rosenthal Test.

†The Serial Bromsulphthalein Test probably would be even more sensitive if a 5 mg. per kilo dose of dye were used.

(c) Comparison\* Serial Bromsulphthalein and Intravenous Hippuric Acid Tests Upon All Clinical Groups—Identical Cases

|   | No. Cases |
|---|-----------|
| Both tests done (various types of cases)                  | 138       |
| Both tests positive                                       | 37        |
| Serial Bromsulphthalein Test alone positive               | 137       |
| Intravenous Hippuric Acid Test alone positive             | 10        |
| Both tests negative—clinical evidence liver disease       | 16        |
| Both tests negative—operative evidence liver disease      | 6         |
| Both tests negative—gall stones—no evidence liver disease | 12        |
| Both tests negative—Misc. (possible liver impairment)     | 14        |

\*Intravenous Hippuric Acid Test yielded positive tests in 51% more cases than the Serial Bromsulphthalein Test.

†Although less sensitive, the Serial Bromsulphthalein Test detected 18 cases of liver impairment not detected by the Intravenous Hippuric Acid Test.

(d) Comparison\* Cephalin-Cholesterol and Intravenous Hippuric Acid Tests Upon All Clinical Groups—Identical Cases

|   | No. Cases |
|---|-----------|
| Both tests done (various types of cases)                  | 62        |
| Both tests positive                                       | 15        |
| Cephalin-Cholesterol Test alone positive                  | 9         |
| Intravenous Hippuric Acid Test alone positive             | 9         |
| Both tests negative—clinical evidence liver disease       | 12        |
| Both tests negative—operative evidence liver disease      | 1         |
| Both tests negative—gall stones—no evidence liver disease | 2         |
| Both tests negative—Misc. (possible liver impairment)     | 14        |

\*These two tests exhibited exactly the same degree of sensitivity in this direct comparison, by yielding the same number of positive tests.

(e) Comparison\* Colloidal Gold and Intravenous Hippuric Acid Tests Upon All Clinical Groups—Identical Cases

|   | No. Cases |
|---|-----------|
| Both tests done (various types of cases)                  | 88        |
| Both tests positive                                       | 24        |
| Colloidal Gold Test alone positive                        | 21        |
| Intravenous Hippuric Acid Test alone positive             | 18        |
| Both tests negative—clinical evidence liver disease       | 14        |
| Both tests negative—operative evidence liver disease      | 0         |
| Both tests negative—gall stones—no evidence liver disease | 1         |
| Both tests negative—Misc. (possible liver impairment)     | 10        |

\*The Colloidal Gold Test yielded positive tests in 7% more cases than the Intravenous Hippuric Acid Test. This figure of 7% greater sensitivity for the Colloidal Gold Test disappears if the 10% of false positive Colloidal Gold Tests in the normal control group are subtracted.

sensitive test was negative. This fact reveals the dissociation of various liver functions. The above two tests constitute two of the three most satisfactory tests studied. One or the other test, or both, were positive in 90 of the 138 cases studied by these two methods.

In subtable (d) of Table IV the cephalin flocculation test revealed exactly the same degree of sensitivity as the intravenous hippuric acid test in the total cases studied by these two methods. The 25% of faintly 1+ cephalin tests were regarded as negative in this comparison. Otherwise the cephalin test would have appeared more sensitive by this direct comparison.

Although the colloidal gold test yielded 7% more positive tests than the intravenous hippuric acid test, as shown in subtable (e) of Table IV, this 7% of greater sensitivity disappears if the 10% of false positive colloidal gold tests, occurring in the normal control group, are subtracted.

TABLE IV (CONTINUED)

(f) Comparison\* Serial Bromsulphthalein and Oral Hippuric Acid Tests Upon All Clinical Groups—Identical Cases

|   | No. Cases |
|---|-----------|
| Both tests done (various types of cases)                  | 57        |
| Both tests positive                                       | 6         |
| Serial Bromsulphthalein Test alone positive               | 12        |
| Oral Hippuric Acid Test alone positive                    | 1         |
| Both tests negative—clinical evidence liver disease       | 11        |
| Both tests negative—operative evidence liver disease      | 6         |
| Both tests negative—gall stones—no evidence liver disease | 13        |
| Both tests negative—Misc. (possible liver impairment)     | 5         |

\*The Serial Bromsulphthalein Test yielded positive tests in 80% more cases than the Oral Hippuric Acid Test. This subtable, however, includes only a small total number of positive tests. Subtables (a) and (c) of this table, both including larger, and therefore more reliable, groups of cases for statistical purposes, suggest that the above figure of 80% of greater sensitivity would be nearer 50% than 80% in a larger group of cases.

(g) Comparison\* Colloidal Gold and Cephalin-Cholesterol Tests Upon All Clinical Groups—Identical Cases

|   | No. Cases |
|---|-----------|
| Both tests done (various types of cases)                  | 124       |
| Both tests positive                                       | 29        |
| Colloidal Gold Test alone positive                        | 27        |
| Cephalin-Cholesterol Test alone positive                  | 17        |
| Both tests negative—clinical evidence liver disease       | 16        |
| Both tests negative—operative evidence liver disease      | 0         |
| Both tests negative—gall stones—no evidence liver disease | 0         |
| Both tests negative—Misc. (possible liver impairment)     | 35        |

\*The Colloidal Gold Test yielded positive tests in 21% more cases than the Cephalin-Cholesterol Test. However, if the excluded one — Cephalin-Cholesterol Tests are included, in order to counterbalance the false positive Colloidal Gold Tests included, there were exactly the same number of positive tests yielded by the two methods.

(h) Comparison\* Cephalin-Cholesterol and Serial Bromsulphthalein Tests Upon All Clinical Groups—Identical Cases

|   | No. Cases |
|---|-----------|
| Both tests done (various types of cases)                  | 82        |
| Both tests positive                                       | 8         |
| Cephalin-Cholesterol Test alone positive                  | 20        |
| Serial Bromsulphthalein Test alone positive               | 13        |
| Both tests negative—clinical evidence liver disease       | 9         |
| Both tests negative—operative evidence liver disease      | 4         |
| Both tests negative—gall stones—no evidence liver disease | 7         |
| Both tests negative—Misc. (possible liver impairment)     | 21        |

\*The Cephalin-Cholesterol Test yielded positive tests in 33% more cases than the Serial Bromsulphthalein Test. If the one + Cephalin-Cholesterol Tests are included in this comparison, the Cephalin-Cholesterol Test yields 53% more positive tests.

(i) Comparison\* Intravenous Hippuric Acid and Rosenthal Bromsulphthalein Tests Upon All Clinical Groups—Identical Cases

|   | No. Cases |
|---|-----------|
| Both tests done (various types of cases)                  | 149       |
| Both tests positive                                       | 28        |
| Rosenthal Bromsulphthalein Test alone positive            | 5         |
| Intravenous Hippuric Acid Test alone positive             | 56        |
| Both tests negative—clinical evidence liver disease       | 17        |
| Both tests negative—operative evidence liver disease      | 8         |
| Both tests negative—gall stones—no evidence liver disease | 21        |
| Both tests negative—Misc. (possible liver impairment)     | 14        |

\*The Intravenous Hippuric Acid Test yielded positive tests in 151% more cases than the Rosenthal Bromsulphthalein Test. This group included many cases from the group of 112 cases presenting definite clinical evidence of liver disease.

The footnotes under subtables (f), (g), (h) and (i) of Table IV explain the interesting features of these subtables. It is of interest to note in subtable (i) that the intravenous hippuric acid test yielded, by direct comparison, *three* times as many positive tests as the Rosenthal bromsulphthalein test, the *least* sensitive of the six tests studied.

For lack of space the other six subtables of Table IV cannot be published. However, they reveal no new essential facts not indicated in the above nine subtables of Table IV.

Briefly, the following essential facts are revealed by the subtables of Table IV. Direct comparisons of one test with another upon the entire group of 307 cases, (presenting slight, moderate and marked degrees of liver impairment), indicate that the intravenous hippuric acid test, the cephalin flocculation test and the colloidal gold test were all very sensitive tests; and exhibited almost exactly the *same* degree of sensitivity. These three tests were *somewhat* more sensitive than the serial bromsulphthalein test, but *much* more sensitive than the oral hippuric acid test or the Rosenthal dye test. The serial bromsulphthalein test is considerably more sensitive than the two older tests.

TABLE V

(a) Incidence of Positive Hepatic Function Tests in Total Group of 112 Cases† with Definite Clinical Evidence of Liver Disease

(Acute Hepatitis, Metastatic Carcinoma of Liver, and Hepatic Cirrhosis)

|                                |      | Positive Tests*     |
|--------------------------------|------|---------------------|
| (1) Intravenous Hippuric Acid  | 75%  | of 56 cases studied |
| (2) Colloidal Gold             | 58%  | of 55 cases studied |
| (3) Cephalin-Cholesterol       | 51%† | of 39 cases studied |
| (4) Serial Bromsulphthalein    | 48%  | of 68 cases studied |
| (5) Oral Hippuric Acid         | 37%  | of 35 cases studied |
| (6) Rosenthal Bromsulphthalein | 25%  | of 71 cases studied |

†About half of the patients in this group presented a slight to moderate degree of liver impairment; and the other half presented marked liver impairment.

\*A direct comparison of the results of successive pairs of tests upon identical cases, in the above group of 112 cases, revealed the *same* order of sensitivity as that indicated above, except that the Cephalin-Cholesterol Test yielded the *same* number of positive tests as the Colloidal Gold Test.

†The per cent of positive Cephalin Tests in this group was 61% if the faintly + tests were included.

(b) Incidence of Positive Hepatic Function Tests in 57 Jaundice Cases. (Non-Obstructive).† (Among 112 Cases with Clinical Evidence of Liver Disease). (Acute Hepatitis, Metastatic Carcinoma of Liver, and Hepatic Cirrhoses — Early and Late Cases)

|                               |     | Positive Tests*     |
|-------------------------------|-----|---------------------|
| (1) Intravenous Hippuric Acid | 89% | of 46 cases studied |
| (2) Cephalin-Cholesterol      | 83% | of 12 cases studied |
| (3) Colloidal Gold            | 72% | of 22 cases studied |
| (4) Oral Hippuric             | 52% | of 19 cases studied |

†This group of jaundiced patients represented, as a whole, the patients with more marked liver impairment in the group of 112 cases. (See Table II). The per cent of positive tests is higher, therefore, for all the tests, than in the total average or mixed group of 112 cases.

The Serial Bromsulphthalein and the Rosenthal Bromsulphthalein Tests were omitted in the jaundiced patients, with an icterus index of 25 or more.

\*A direct comparison of the results of successive pairs of tests upon identical cases, within the above group of 57 cases, revealed the *same* order of sensitivity as that indicated above.

(c) Incidence of Positive Hepatic Function Tests in Hepatic Cirrhosis Group Without Ascites.\* (Enlarged liver associated with either alcoholic history or evidence of gall tract disease, or both) (52 cases studied)

|                                |     | Positive Tests      |
|--------------------------------|-----|---------------------|
| (1) Intravenous Hippuric Acid  | 66% | of 38 cases studied |
| (2) Colloidal Gold             | 50% | of 30 cases studied |
| (3) Cephalin-Cholesterol       | 48% | of 23 cases studied |
| (4) Serial Bromsulphthalein    | 41% | of 37 cases studied |
| (5) Rosenthal Bromsulphthalein | 20% | of 39 cases studied |
| (6) Oral Hippuric Acid         | 19% | of 16 cases studied |

\*The cases in this group represent slight and moderate degrees of cirrhosis in the hypertrophic stage. The per cent of positive tests is lower, therefore, for all the tests, than in the total mixed group of 112 cases.

INCIDENCE OF POSITIVE HEPATIC FUNCTION TESTS IN VARIOUS GROUPS OF PATIENTS WITH KNOWN HEPATIC DISEASE

In subtable (a) of Table V, including the entire 112 cases with definite clinical evidence of liver disease, the relative *per cent* of positive tests obtained with each of the six tests *coincides* almost exactly with the relative *degree* of sensitivity of the six tests as determined by direct comparison of one test with another in Table IV.

The only exception to the above statement regarding the *relative* sensitivity of the various tests involves the *intravenous* hippuric acid test. In the 112 cases with clinical evidence of liver damage, referred to in Table V (a), and in all the subgroups of cases within this larger group of 112 cases reviewed in subtables (b), (c) and (d) of Table V, the intravenous hippuric acid test yielded *more* positive tests, and exhibited somewhat greater sensitivity than the cephalin flocculation and colloidal gold tests.

However, in the total group of 127 cases of proven and probable gall stones, and in the *miscellaneous* group of 68 cases, where, on the whole, a lesser degree of liver impairment existed, the cephalin test and the colloidal gold test were somewhat more sensitive than the intravenous hippuric acid test.

The above two facts explain why the intravenous hippuric acid test happens to yield almost exactly the *same* number of positive tests as the cephalin and colloidal gold tests in the *total* group of 307 cases.

TABLE V (CONTINUED)

(d) Incidence of Positive Hepatic Function Tests in Total Sub-Group of Portal Cirrhosis Cases with Ascites\*

| No. | I.V. Hippuric | Oral Hippuric | Serial Bromsulphthalein | Coll. Gold |
|-----|---------------|---------------|-------------------------|------------|
| 1   | .55 gm.       | 3.79 gm.      | 35-12- 8- 5-Tr- 0       |            |
| 2   | .58 gm.       |               | 45-10-10- 0- 0- 0       |            |
| 3   | .81 gm.       | 3.32 gm.      | 35-20-15- 5- 0- 0       | 534        |
| 4   | .57 gm.       |               | 50-40-40-25-25-15       | 533        |
| 5   | .62 gm.       |               | 55-15- 5- 0- 0- 0       |            |
| 6   | .62 gm.       | 3.8 gm.       | 55-15- 5- 0- 0- 0       |            |
| 7   | .48 gm.       |               |                         |            |
| 8   | .20 gm.       |               |                         |            |
| 9   | .68 gm.       |               | 55-15- 5- 0- 0- 0       | 432        |

\*5 cases (89%) yielded a positive Intravenous Hippuric Acid Test. 3 of 7 cases (43%) yielded a positive Bromsulphthalein Test. Only a few serological tests were done on this small group of cases with a late stage of cirrhosis.

(e) Incidence of Positive Hepatic Function Tests in the Proven Cholelithiasis Group (67 Cases)\*. (Studies Conducted Before Operation)

|                                |      | Positive Tests      |
|--------------------------------|------|---------------------|
| (1) Colloidal Gold             | 63%† | of 19 cases studied |
| (2) Intravenous Hippuric Acid  | 53%  | of 47 cases studied |
| (3) Cephalin-Cholesterol       | 50%† | of 17 cases studied |
| (4) Serial Bromsulphthalein    | 45%  | of 52 cases studied |
| (5) Rosenthal Bromsulphthalein | 15%  | of 60 cases studied |
| (6) Oral Hippuric Acid         | 6%   | of 15 cases studied |

\*The interesting feature of this table is the proof that evidence of liver impairment can be demonstrated in a substantial per cent of gall stone cases with the newer, more sensitive tests.

†A direct comparison upon identical cases indicates that the Intravenous Hippuric Acid Test was *more* sensitive than the Colloidal Gold Test in this group of cases. The Colloidal Gold figure of 63% evidently contains some false positive tests, as did normal control series.

‡This figure of 50% does not include the faintly positive (one +) Cephalin-Cholesterol Tests.

§This low figure of 6% is not significant because of the small number of cases studied.



The exact per cent of positive tests obtained with all six methods was *higher*, for obvious reasons, in the groups of cases with a *more marked* degree of liver disease than in the presence of less marked hepatic impairment. This fact is illustrated in the various subtables of Table V. For example, a higher per cent of positive tests was obtained in the jaundice and late cirrhosis groups; whereas a somewhat *lower* per cent occurred in the early cirrhosis and gall stone groups. On the other hand, the per cent of positive tests in the *mixed* group of 112 cases, containing both early and late cases, was *average*, or intermediate in character.

TABLE VI  
Results of tests in individual typical cases\*

| Case                  | I.V.<br>Hippuric<br>Acid | Serial<br>Bromsulphthalein | C.G. | C.C. |
|-----------------------|--------------------------|----------------------------|------|------|
| 1. Carcinoma of Liver | .56                      | 50 80 20 20 20 20          | 551  | 3 -  |
| 2. Carcinoma of Liver | .41                      | 80 10 30 5 0 0             | 532  | 0    |
| 3. Carcinoma of Liver | .50                      | 20 5 0 0 0 0               | 543  | 1+   |
| 4. Carcinoma of Liver | .62                      | 22 7 0 0 0 0               | 554  | 0    |
| 5. Carcinoma of Liver | .50                      | 35 10 Tr 0 0 0             |      |      |
| 6. Hepatic Cirrhosis  | .61                      | 40 15 5 0 0 0              | 543  | 3--  |
| 7. Hepatic Cirrhosis  | .57                      | 50 10 40 25 25 15          | 533  |      |
| 8. Hepatic Cirrhosis  | .72                      | 15 15 5 0 0 0              | 432  | 3+   |
| 9. Hepatic Cirrhosis  | .69                      | 55 30 10 0 0 0             | 332  | 1+   |
| 10. Hepatic Cirrhosis |                          | 50 35 30 30 15 0           | 553  | 1+   |
| 11. Hepatic Cirrhosis | .09                      | 50 20 10 5 Tr 0            | 433  | 0    |
| 12. Cholelithiasis    | .73                      | 50 25 10 10 0 0            | 533  | 0    |
| 13. Cholelithiasis    | .41                      | 50 30 5 0 0 0              | 432  | 2--  |
| 14. Cholelithiasis    | .19                      | 35 25 Tr 0 0 0             | 433  | 0    |
| 15. Cholelithiasis    | 1.02                     | 27 3 Tr 0 0 0              | 532  | 4+   |
| 16. Cholelithiasis    | .49                      | 40 20 Tr 0 0 0             | 543  | 1--  |
| 17. Cholelithiasis    | .89                      | 70 30 15 5 0 0             | 513  |      |
| 18. Cholelithiasis    | .56                      | 40 Tr 0 0 0 0              | 543  | 3+   |
| 19. Acute Hepatitis   | .55                      |                            | 431  | 1+   |
| 20. Acute Hepatitis   | .56                      |                            | 553  | 2+   |
| 21. Acute Hepatitis   | .96                      |                            | 443  | 1+   |

\*Only two of the above patients yielded a positive result with all four of the newer tests. Three patients upon whom only three tests were conducted yielded positive results with these three tests. The other sixteen of the twenty-one cases illustrate varying degrees and types of dissociation of results of the four newer tests. One would expect this dissociation.

The findings in Table V (e), dealing with evidence of impaired liver function in cases of *cholelithiasis* are of especial interest. The work of Evarts Graham and others, has demonstrated that some degree of impaired liver function must exist in many cases with cholelithiasis. This is the only reasonable explanation for the appreciable reduction of post-operative mortality occurring after cholecystectomy, when patients are consistently given a high carbohydrate intake for a period before operation. And yet the oral hippuric acid and Rosenthal dye tests have demonstrated preoperative evidence of this impairment in only a *small* percentage of cases. The fact that the *newer*, more *sensitive* tests show preoperative evidence of impaired liver function in over 50% of the cases is of practical importance in *selecting* those cases needing *special*

preoperative preparation. In most of these cases, the positive tests, with the more sensitive methods, become negative with proper preoperative preparation. Ravdin and others have emphasized that proper preoperative preparation includes not only a high carbohydrate intake, but also a high normal protein intake and a very *low* fat intake.

In the *unoperated* cholelithiasis group, which clinically suggested a *lesser* degree of liver impairment than the operated group, the per cent of positive tests with the newer methods was *not* nearly so high as in the *operated* group studied before operation. In other words, the exact per cent of cholelithiasis cases showing evidence of hepatic impairment will *vary* considerably in different groups of cholelithiasis cases.

In Table VI typical results of the four newer liver function tests upon 21 *individual* cases are tabulated. Space does not permit tabulating the individual results upon the *entire* 307 cases.

Table VI illustrates two important facts. In the first place, it portrays the *dissociation* of the results of different liver function tests. In these 21 individual cases there is every conceivable *combination* of positive and negative results among the four methods. In liver disease, one function of the liver may be impaired without demonstrable abnormality of another function. In the second place, Table VI illustrates the practical importance of not relying upon *any one* liver function test for evaluating liver function, no matter how sensitive and reliable that one test may be. At least *several* hepatic function tests should be utilized, if one expects to *demonstrate* impairment of liver function in the highest possible per cent of those cases having impairment.

#### ADVANTAGES AND LIMITATIONS OF EACH TEST

##### I. Intravenous Hippuric Acid Test.

###### (a) Advantages.

- (1) Combines marked sensitivity with reliability.
- (2) Is applicable to jaundiced and non-jaundiced cases.
- (3) Measures maximum hepatic work for a short period, and directly tests a synthetic and a detoxifying function.

###### (b) Limitations.

- (1) Dehydration, nephritis, or urinary tract obstruction may retard the elimination of synthesized hippuric acid, and may result in a low output. (This should not be confusing, however, since the above conditions are easily recognized).

##### II. Cephalin-Cholesterol Flocculation Test.

###### (a) Advantages.

- (1) Combines marked sensitivity with reliability, provided either *ripened* cephalin is used, or else the false faintly positive 1+ reactions are regarded as negative.
- (2) Applicable to jaundiced and non-jaundiced cases.
- (3) +, ++, +++ and ++++ readings afford a quantitative test as to the degree of liver impairment.

(4) Involves the simplest technique of all six tests.

(b) Limitations.

(1) None apparent.

### III. Colloidal Gold Test.

(a) Advantage.

(1) Possesses marked sensitivity.

(b) Limitations.

(1) As a *routine* laboratory test, it is complicated, time-consuming, and susceptible to false positive tests, because of considerable *variation* in the colloidal gold readings upon the serum of various *normal* individuals.

(2) To avoid false positive tests and to render the test reliable, it is important to conduct tests upon 10-20 normal control sera *every two weeks*, when restandardizing the gold solution for its new acid requirement.

### IV. Serial Bromsulphthalein Test.

(a) Advantages.

(1) Rather sensitive and very reliable.

(2) Tests a detoxifying function of liver.

(b) Limitations.

(1) Not applicable or accurate in presence of jaundice.

*Comment:* It is probable that the sensitivity of this test can be increased still *further* by increasing the dose of the dye from 2 mg. to 5 mg. per kilo body weight, as recommended by Macdonald. The criteria for normal and abnormal readings with this larger dose, using the serial method, are being determined by the authors.

### V. Oral Hippuric Acid Test.

(a) Advantages.

(1) Is a simple, reliable and inexpensive test.

(2) Has a *proven* value in determining the *operability* of patients with liver damage. Less than 50% of normal hippuric acid excretion, viz., less than 1.5 gms. excretion in 4 hours, indicates a *poor* operative risk.

(b) Limitations.

(1) Is less sensitive than the newer tests in demonstrating early hepatic impairment.

### VI. Rosenthal Bromsulphthalein Test.

(a) Advantages.

(1) Is very reliable when positive.

(b) Limitations.

(1) Lack of sensitivity, and the lack of any advantage over the much more sensitive, and at the same time reliable, *serial* bromsulphthalein test.

*Comment:* This test should be *replaced* by the *serial* method.

### SUMMARY

(1) A comparative statistical study has been conducted to determine the *sensitivity* and *reliability* of Quick's *intravenous* hippuric acid test, a modification of Macdonald's *serial* bromsulphthalein test, Hanger's cephalin-cholesterol flocculation test and Gray's colloidal gold test, in relation to each other, and to the two older tests, viz., the *oral* hippuric acid test and the Rosenthal bromsulphthalein test.

(2) The *literature* dealing with each of the six tests has been reviewed in some detail.

(3) The exact *method* employed for each test has been outlined.

(4) Normal *control* studies have been conducted upon 40 healthy young individuals, employing the four newer liver function tests. (See Table I). No *false* positive tests occurred in using the intravenous hippuric acid test or the *serial* bromsulphthalein test. There were 12½ per cent of false, *faintly* positive, *one +* results with the cephalin-cholesterol flocculation test; but there were *no ++, +++*, or *++++* cephalin results in this normal group. The *one +* cephalin results in the *patients* subsequently studied were regarded, therefore, as not indicating liver impairment; and they were excluded from the statistical tables. Ten per cent of the colloidal gold tests in this normal control group displayed a definite *false* positive result. Since it was not possible to *identify* the individual false positive colloidal gold tests in the group of *patients* subsequently studied, no correction could be made in the statistical tables for the 10% of false positive colloidal gold results.

(5) The *clinical material* utilized for this study consisted of (1) 112 patients with definite *clinical* evidence of different types and degrees of liver disease; (2) 127 patients with cholelithiasis, and (3) a *miscellaneous* group of 68 patients; or a *total* of 307 patients. Groups (2) and (3) did not include cases with direct clinical evidence of liver impairment, but offered a probable source of a number of cases with *earlier* hepatic impairment than group (1). (See Table II for details).

(6) A total of 1013 hepatic function tests, distributed among the six methods, were conducted upon 307 *private* patients, an *average* of slightly more than three tests per patient. (See Table III). Satisfactory *comparative* data was thus obtained, even though it was not feasible to conduct all six tests upon each patient. Each method was compared individually with each of the other five methods upon identical cases.

(7) In Table IV are published the 9 most important of the 15 subtables, which compare each test with each of the other 5 tests. A *direct comparison* of successive pairs of tests upon groups of identical cases, taken from all three clinical sub-groups of the total group of 307 cases, indicates that the *intravenous* hippuric acid test, the cephalin-cholesterol flocculation test and the colloidal gold test were all three very *sensitive* tests; and they exhibited almost exactly the *same* degree of sensitivity. These three tests were *much more* sensitive than the oral hippuric acid or Rosenthal bromsulphthalein tests. The *serial* bromsulphthalein test was somewhat less sensitive than the other three newer tests, but considerably *more* sensitive than the two older tests.

(8) Subtables (a), (b), (c), (d) and (e) under Table V reveal the percentage *incidence* of *positive* tests with each method, when employed in clinical groups of cases with different types and degrees of liver impairment. This table confirms the findings of Table IV as to the relative sensitivity of the six tests. The *incidence*, with the newer and more sensitive tests, of preoperative evidence of hepatic impairment in the operated cholelithiasis cases is of especial inter-

Another thing I think should be emphasized in relation to liver function tests, is that the organ is dynamic and



not static. Too often I think the clinician when he says something in regard to liver function, feels it is definite and fixed, which is not true, because liver function varies not only from day to day but also from hour to hour.

Another thing which should be borne in mind in obtaining control data, is that adequate provision should be made in regard to the diet and the period of withdrawal of food before the test. I think that is very important because we know we can take animals and put them on a diet high in one food substance and obtain one result and if we put them on another foodstuff, obtain an entirely different result.

There are many other factors that must be considered. For instance if the substance of which we heard in one paper; stilbestrol is given to fowl, the fat content of the liver may increase to as much as thirty or forty per cent within a few hours, an occurrence which will greatly affect the functions of the organ and will surely affect the liver function test.

Finally I just wish to emphasize, first, the fact that the type of clinical research that is being done on the liver in relation to functional tests is greatly improved, and these papers are an excellent example illustrating that improvement; second, in regard to evaluating any test, the clinician must remember that the liver is dynamic and not static, and the result of a test today doesn't mean it will be the same tomorrow; and, third, that in view of the fact that the liver is dynamic, that it is affected by so many things, particularly intake of foods and so forth—all such factors should be taken into consideration, particularly in obtaining your control data.

**DR. FRANKLIN W. WHITE (Boston, Mass.):** We have plenty of liver function tests to choose from, and apart from research, it seems wiser in clinical work to choose tests which are *relatively easy to do* rather than those which are quite difficult. Our experience with liver function tests has shown that ester cholesterol estimations were more difficult in the laboratory and had a greater percentage of error than most of the other tests.

We use liver function tests to detect liver damage and also, if possible, to differentiate different types of hepatic disease; and, if very sensitive tests are used in order to pick up minimal degrees of liver damage, we cannot expect much differential value in such tests; for example, the bromsulphthalein or hippuric acid tests are so sensitive that they are abnormal in almost all types of liver disease and cannot be used in differential diagnosis.

It seemed possible that if we step up the sensitiveness of the oral galactose tolerance test, so that, for example, instead of getting 25 per cent abnormal results in cirrhosis, we get 85 per cent abnormal, the test might lose something in differential value.

More information is very welcome regarding the cephalin-cholesterol flocculation test, which seems easy to do, for the present reports are somewhat contradictory. Hanger, in obstructive jaundice, finds about 9 per cent positive, and Pohle and Stewart follow him a year or so later and find 78 per cent, and Dr. Mateer has just shown us about 48 per cent positive—there seems to be too much variation in this test at present.

I was not able to grasp Dr. Rosenberg's idea that hyperexcretion of hippuric acid was so valuable a sign of mild liver disease, when anything above three grams has been considered as being normal, and less than that abnormal. Shall we also think of more than three grams as being abnormal?

**DR. ABRAHAM LEON GARBAT (New York City):** In cases of jaundice we must differentiate between two objects: first, the use of various tests advocated to measure the functional capacity of the liver; and, second, the use of these various procedures to diagnose clinically whether a case of jaundice is going to be benefited by

surgical intervention or not. If these two objects in view are not strictly differentiated, a great deal of disappointment and false conclusions are inevitable. No single test should be taken for such an absolute differentiation.

Four years ago I presented before this Association a glucose tolerance test which was worked out by my associate, Dr. Jacobi, on my service at the Lenox Hill Hospital, New York. Since then we have continued and broadened its use and it has become our routine method as a differential aid between the surgical and non-surgical cases of jaundice.

It is performed as follows: The patient with jaundice is given 100 grams of glucose orally and blood sugar determinations are made before he takes the sugar, one hour afterwards and two hours afterwards. Any case in which the blood sugar curve showed a return to the normal level at the end of the two-hour period, denoted jaundice of toxic origin, in which instance operative interference should not be undertaken. This group includes cases of the so-called catarrhal jaundice or infectious jaundice or non-obstructive or medical jaundice, or parenchymatous jaundice (Figs. 1 and 2).

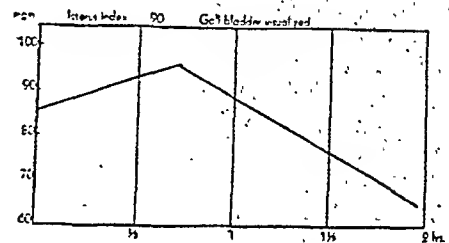


FIG. 1. Sugar tolerance curve.

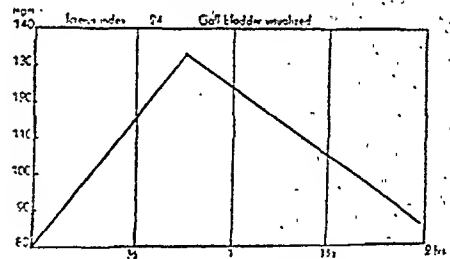


FIG. 2. Sugar tolerance curve.

On the other hand, cases of jaundice in whom the blood sugar curve at the end of the two-hour period, failed to return to normal, indicated that the jaundice was due to some form of obstruction of the bile, either (1) obstruction of the common bile duct by stricture, suppuration, calculus, carcinoma of the common duct, carcinoma of the head of the pancreas; or (2) some intrinsic hepatic disease giving bile obstruction, such as cirrhosis, carcinoma, or abscess (Figs. 3, 4 and 5).

From the surgical point of view, however, not all the cases with this so-called obstructive blood sugar curve, are to be benefited by surgery. In order to further help us, in this differentiation, a therapeutic test was devised in association with the glucose tolerance test; namely: All cases of jaundice are placed on a high carbohydrate diet plus 250 grams of glucose orally, in the form of lemonade; in addition, ten units of insulin are given twice a day, and an intramuscular injection of liver extract, about 3 cc. of the dilute liver extract, given once a day.

With the use of this regimen, kept up for two or three weeks, the cases of obstructive jaundice which are due to

benign lesions of the liver and which would not benefit by surgery, such as cirrhosis, reacted by a gradual decrease in the degree of icterus. The other group of cases, that failed to improve by this routine were found to be due either to calculus in the common bile duct, or carcinoma of the head of the pancreas, or carcinoma of the liver, and thus merited surgical exploration.

In summary, therefore, jaundice cases whose blood sugar curves fall into Groups 1 or 2 are considered to be due to purely toxic causes and hence surgical interference is ruled out; however, cases with curves similar to 3, 4 and 5 are cases where surgical jaundice should be suspected. If all the other available data, clinical and laboratory, still make one doubtful as to the exact mechanism of

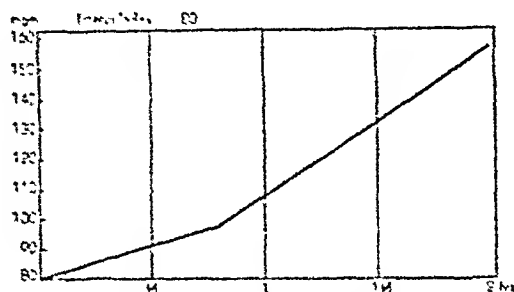


FIG. 3. Sugar tolerance curve.

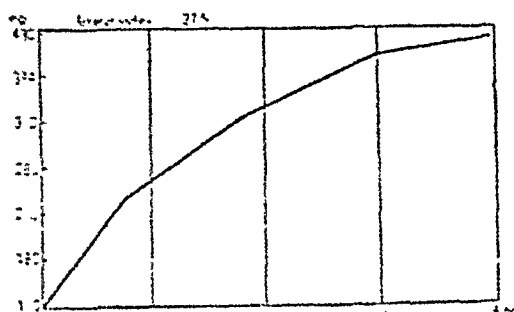


FIG. 4. Sugar tolerance curve.

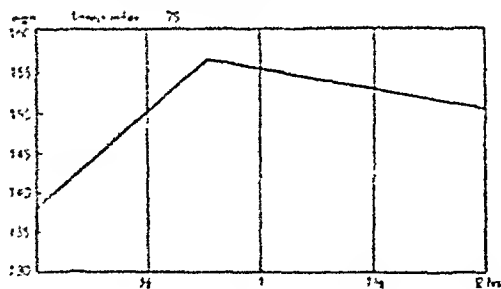


FIG. 5. Sugar tolerance curve.

the jaundice in these last groups of cases, it is far safer to adopt the conservative method of administering to such patients 250 grams of glucose, 10 units of insulin twice a day, and 3 cc. of liver extract once a day.

If at the end of several weeks' treatment the degree of icterus has remained unchanged or has increased, the lesion has reduced itself to one of calculus of the common duct or carcinoma of the head of the pancreas or liver and surgical intervention is justified.

DR. ISAAC R. JANKELSON (Boston, Mass.): I just want to limit myself to discussing Dr. Althausen's paper. In 1934 and again in 1937 we have recorded our findings in intravenous galactose liver function tests using 25 grams of galactose without consideration of the weight of the patient.

Before that, in 1932, Pollack used intravenous galactose liver tests using 8 grams galactose without consideration of the weight of the patient.

Now I want to just record that in a large percentage of the cases where intravenous galactose tests are used, a variable amount of galactose appears in the urine.

Since Dr. Pollack's work did not differentiate between the galactose and the total reducing substances in the blood, we cannot draw any direct analogy between our work and his, but we can use his data as to the amount of galactose secreted in the urine; when using 8 grams of galactose, the maximum in his cases was 0.8 gram in the urine, which is 10 per cent. This represents the error of the test. While using 25 grams of galactose, up to 5 grams appeared in the urine irrespective of the weight of the patient, representing a 20 per cent error.

Now Dr. Althausen proposes a graded amount which essentially represents an increased amount of galactose given intravenously, and since he is giving 25 grams for 50 kilo body weight and 35 grams for 70 kilo weight, by analogy I should expect there would be a greater amount of galactose secreted in the urine, and therefore a greater source of error.

I have no objections to graded doses, but I should say the maximum amount that should be used would be from 12 to 15 grams per patient, and not 25 and above.

DR. ARTHUR T. ATKINSON (Chicago, Ill.): I would like to confirm Dr. Rosenberg's observation of the apparent biphasic action of the hippuric acid excretion test. In a study of some gouty individuals, I obtained hyperexcretion occasionally in patients with gout and mild liver damage. In the great majority of patients the hippuric acid excretion was within normal limits. I was very much interested to hear Dr. Rosenberg's explanation of that action.

DR. HENRY J. TUMEN (Philadelphia, Pa.): I wish particularly to ask Dr. Rosenberg for some clarification about the point raised by Dr. White. The mechanism of the hippuric acid test is assumed to be conjugation by the liver of the benzoic acid radicle with glycine to form hippuric acid, and the amount formed is supposed to be dependent on the amount of glycine available in the liver. Dr. Rosenberg's statement implies that there are certain phases of liver dysfunction during which there is more than a normal amount of glycine available in the liver.

I wonder if that viewpoint is justifiable. In our own experience it hasn't been unusual to find patients who normally excrete more than the amounts of hippuric acid usually considered normal. There was a patient like that listed in Dr. Mateer's chart, and such patients usually excrete more than the "normal" amount of hippuric acid when the test is done repeatedly. They are not any more abnormal in that respect than if they had more than 100 per cent of hemoglobin. I wonder if the particular patients whom Dr. Rosenberg considered as showing hyperexcretion continued to do that later, and whether, if they had been examined repeatedly, it might not have been found that they always responded by having more than the usual amount of hippuric acid excretion.

DR. HARRY SHAY (Philadelphia, Pa.): Mr. President, Dr. Althausen said that he thought the galactose test the ideal test for the carbohydrate function of the liver. I am completely in accord with that statement. However, with the implication that the mouth procedure for the galactose tolerance test was not found to be of much clinical use, I cannot agree.

As I look over this audience, I see a number of faces of men who have reported on the mouth procedure, Franklin White of Boston, Rosenberg of Chicago, Schiff of Cincinnati, and Tumen of Philadelphia. I think if we take their

results, forgetting our own for the moment, the mouth method compared with the intravenous method of Dr. Althausen does not come off badly. Urine galactose can be readily determined even in deeply pigmented urine by first clearing the urine. Furthermore I think we should limit the use of liver function tests for those purposes for which they have been found of value.

Thus, the galactose tolerance test is of value in differentiation of hepato-cellular jaundice from obstructive jaundice and is not a test for liver function in general. If applied for the latter purpose, it will certainly fall down.

I believe Dr. Bauer made the mistake originally in applying the test for cirrhosis, and since then the test has suffered a black eye because he tried to stretch the value of the test to a point it could not reach.

Dr. Mann has given us the crux of the whole liver function problem; namely, that it is a dynamic and not a static one, a fact especially true during jaundice. With that idea in mind we have practiced and urged repetition of tests at short intervals, thus judging the changing picture that is so often present.

I would like to ask Dr. Althausen if he has any parallel results, that is, the mouth test and the intravenous test done on the same patient within a very short interval of each other.

Thank you.

DR. DAVID H. ROSENBERG (Chicago, Ill.) (closing the discussion): I wish to thank the discussants for their interesting and thought-provoking comments.

I am happy that Dr. Jones brought up the matter of the discrepancies that appear in the literature concerning the range of normal values for cholesterol. I believe that his remarks explain the many differences of opinion which exist at this time.

As was commented upon earlier, we used blood serum for our determinations of the ester and total cholesterol, and selected the range of normal which is well within the limits described and illustrated by Dr. Jones.

Dr. Mateer and his associates used the original bromsulphthalein test, carrying out the procedure with the 2-milligram dose. We, however, used the 5-milligram dose and observed the retention at the end of thirty minutes.

The difference which Dr. Mateer reported in his studies with the flocculation test may well be explained on the basis of the fact that he disregarded the slight degrees of flocculation, that is, one-plus or less. In the beginning of our work with this test, we were concerned about the significance of this amount of flocculation, and therefore made extensive, comparative studies with other tests of liver function, and, in addition, with double glucose tolerance tests. We concluded that any degree of flocculation, even though one plus or plus-minus, is indicative of liver damage. As to its clinical significance, that must be correlated with the clinical observations and the clinical findings.

We also found early in our work that the freshly prepared form of sheep brain cephalin may give unreliable results owing to its extraordinary sensitivity. We further observed that if the cephalin remained exposed to the air for a number of weeks, there is a difference in the color of the sheep brain cephalin. These points are included in our paper, but for the sake of brevity in the presentation, I could not mention them. The oxidized cephalin gives reliable results and therefore slight degrees of flocculation should not be disregarded.

Previously, at a meeting in Chicago, we advocated its routine use in studies pertaining to digestive disturbances with particular reference to liver disease.

I can echo the opinion of Dr. Mateer with regard to the colloidal gold test. We have not found it sufficiently reliable to warrant the difficulties in preparing adequate control material. Further it does not yield a quantitative result.

With few exceptions, all of our hippuric acid tests were performed in accordance with the original oral method.

In reply to Dr. Tumen and Dr. White, I might say that as early as 1937 we observed some cases in which definite liver disease was accompanied by hyperexcretion of hippuric acid, and we have since been very much interested in its significance. Recently, in the March issue of the American Journal of Clinical Pathology, 1940, Quick also stated that he is of the opinion that hyperexcretion of hippuric acid is probably a manifestation of abnormal liver function. The matter of interpretation of the hyperexcretion of hippuric acid is in doubt at the present time. Experimental work has shown that toxic agents which damage the liver first produce an increase in the irritability of the liver, and thereby augment the rate at which this organ performs its various functions. We have suggested, therefore, that hyperexcretion may by analogy be another manifestation of the hyperirritable phase.

We have performed repeated hippuric acid tests on patients showing the hyperexcretion phenomenon, and have observed the same results except in a few patients recently studied, who had been placed on therapy directed to the improvement of liver function. The latter patients have shown a return to the normal excretion of hippuric acid.

Thank you!

DR. CHARLES A. JONES (Philadelphia, Pa.) (closing the discussion): There are two additional points I should like to make. One is the fact that in our material we couldn't distinguish them in groups by means of concentrations of various plasma lipids, and know whether or not the obstruction of the biliary passage was strong. The range such as it was was so large that in either of the two groups, when considering the groups, we couldn't distinguish the two.

The second point is the fact that in the obstructive cases the increased ratio of free to total cholesterol apparently didn't have the same significance as indicated severity of hepatic damage, as it did in cases that weren't obstructive. In the non-obstructive cases almost all those who had in excess of 60 per cent free cholesterol died. That was not true of those with obstructive jaundice. Neither was cholesterol with albumen in the patients in the group of obstructive jaundice as is present in the cases with hepatic diseases.

DR. JOHN G. MATEER (Detroit, Mich.) (closing the discussion): We agree fully with Dr. Mann's emphasis upon the dissociation of different liver function tests. Because of limited time, we were unable to show our lantern slide tables of the results of the four liver function tests in individual cases. These tables of individual cases show in a striking manner the dissociation of the results of the different tests. A survey of these tables reveals the need, therefore, of performing at least several tests in each case, rather than conducting only the single test which yields the highest per cent of positive results in a group of cases.

Dr. White's inquiry about the different statistical results obtained by different workers with the cephalin test is a very reasonable question. In this study we have made no attempt to use this test to differentiate obstructive and hepatogenous jaundice. We have used the test simply as an index of impairment of hepatic function, regardless of whether the patient was jaundiced or not. (As a matter of fact, no obstructive jaundice cases were included in this clinical material). Hanger, in his second paper, and Pohle and Stewart in their recent communication attempted to evaluate the cephalin test as a method to differentiate the two common types of jaundice. The difference in their experience, we believe, was due, at least in part, to the fact that Hanger's jaundiced patients, as a group, were studied

at a somewhat *earlier* stage in the course of the jaundice. So much depends upon the *duration* of the jaundice when the test is performed, that no *liver function* test should be expected to serve as a *final* differential criterion between hepatogenous and obstructive jaundice. The earlier any liver function test can be conducted in the course of jaundice, the more reliable will be its differential aid.

We agree with Dr. Rosenberg's *explanation* of the apparent differences between his experience and ours with the cephalin test. Evidently he has been using *ripened* cephalin. We have used *unripened* cephalin, following Hanger's published technique. Hanger's more recent suggestion to use ripened cephalin represents an improve-

ment in the method. The need is thus eliminated for *excluding* the 25 per cent of *faintly* positive one + results from the total positive results obtained with *ripened* cephalin. According to Hanger, *false* faintly positive reactions upon *normal* subjects do not occur with *ripened* cephalin.

As to the optimum dose of bromsulphthalein for evaluation of liver function, Macdonald's recent experiments would suggest that the 5 mg. dose per kilo provides a more sensitive test than the 2 mg. dose. However, regardless of which dose may be selected, the employment of the *serial* method will *increase* the sensitivity of the test.

## The Genesis of Pellagra, Pernicious Anemia and Sprue\*

By

SEALE HARRIS, M.D.

and

SEALE HARRIS, JR., M.D.

BIRMINGHAM, ALABAMA

WE do not believe that pernicious anemia, pellagra, and sprue are different manifestations of the same disease, but, on the contrary, it is evident that they are three separate and distinct disease entities. There are, however, symptoms which may be common to the three diseases, including all the gastro-intestinal symptoms, nervous manifestations, and macrocytic anemia. For instance, given an adult patient with achlorhydria, stomatitis, diarrhea, mental depression, and the motor manifestations resulting from involvement of lateral and posterior columns of the spinal cord and severe anemia, without skin lesions, it may be impossible to make a positive diagnosis of pellagra, pernicious anemia, or sprue. The addition of a symmetrical, bilateral, pigmented, exfoliative, erythematous dermatitis of the dorsal surfaces of the hands and feet to symptoms which may be common to sprue and pernicious anemia enables the clinician to make a diagnosis of pellagra; while the large, fatty, fermenting pasty, clay-colored stools in a patient with stomatitis, diarrhea, and severe anemia, may be the only pathognomonic difference between sprue and pernicious anemia. The patient with stomatitis, diarrhea, mental, sensory and motor symptoms, and anemia without skin lesions who resides in a community in which pellagra exists would be regarded as a probable pellagrins. Likewise the patient with the same symptoms, who resides for instance in Porto Rico in which sprue is endemic, with only an occasional case of pellagra, would be diagnosed as having sprue.

*Gastro-Intestinal Symptoms in Pernicious Anemia.* Richard Cabot said that diarrhea was present in the majority of his cases of pernicious anemia; and the Boston patient with macrocytic anemia, stomatitis, diarrhea, and the nervous manifestations common to these three chronic diseases would be diagnosed as a victim of typical Addisonian anemia.

William Murphy's description of the gastro-intestinal tract symptoms of pernicious anemia in his new

book (1939) on "Anemia" (p. 89) might apply as well to the subclinical type of pellagra before skin lesions appear as when there are no skin lesions present. He mentions as symptoms of pernicious anemia "sore tongue or sore mouth, diarrhea, anorexia, nausea and vomiting, and achlorhydria." All of these symptoms also occur in pellagra. Mental symptoms are frequent in pellagra, and less frequent in pernicious anemia. Murphy, in discussing psychoses in pernicious anemia, said that psychotic symptoms may occur when the red blood counts are low.

When the diagnosis of pernicious anemia, pellagra, or sprue is made, the treatment found most effective in all of them is liver, or liver extract and a high protein, relatively low carbohydrate, rich vitamin diet—practically the only difference being that in pernicious anemia liver or liver extract must be continued for the rest of the patient's life.

*Similar Pathology in Pellagra, Pernicious Anemia, and Sprue.* In the great majority of cases there is pronounced liver pathology, fatty degeneration usually, in pellagra, pernicious anemia, and sprue.

A number of writers have called attention to the changes in the liver in pellagra; and it is enough to cite Sir William Osler as saying that in pernicious anemia "the liver may be enlarged and fatty. In most of my autopsies it was normal in size, but usually fatty." Atrophy of the stomach may be seen in all three diseases, and the permanent subacidity and anachlorhydria are evidences of damage to the hydrochloric acid-forming cells in the stomach in pellagra, sprue, and pernicious anemia. Atrophy of the intestines may be seen in all three diseases. Likewise, there is marked similarity in the pathology of the lateral and posterior columns when there are cord changes in pernicious anemia, pellagra, or sprue.

The food factor, a deficiency diet, certainly is much the same in the etiology of pellagra and sprue, and to a less extent in pernicious anemia. The etiology of pernicious anemia is admittedly unknown, Ashford's theory of the *Monilia psilosis* is not generally accepted as being the cause of sprue, and while many believe

\*Read at the Forty-Fourth Annual Meeting of the American Gastro-Enterological Association, Atlantic City, N. J., May 6, 1941.

that a deficiency of nicotinic acid is the cause of the symptoms of pellagra, all of the essential factors in the production of pellagra have not been discovered. It certainly seems that it would be advisable to continue investigations into the causes of pernicious anemia, pellagra, and sprue until all the etiologic factors in each have been recognized.

*Intrinsic Liver Factors in Pernicious Anemia and Pellagra.* At the meeting of the Mississippi State Medical Association in May, 1927 (New Orleans M. & S. J., Sept., 1927) I submitted data predicating the hypothesis that pernicious anemia is essentially a disease of the liver and that pathology of the stomach, resulting in achlorhydria, is an etiologic factor of, or a concomitant condition associated with, macrocytic anemia. I then suggested the possibility that the liver, in addition to its many other functions, may be an endocrine organ, secreting hormones which control erythrocytolysis and, or, hematopoiesis.

Accumulated data showing almost constant pathology of the liver in pellagra and pernicious anemia and the use of liver and liver extracts in the treatment of both diseases seem to be sufficient basis for considering the possibility that the liver and the stomach may secrete synergistic hormones, a deficiency of either one of which results in pernicious anemia; and that liver damage prevents the utilization or storage of nicotinic acid, the cause of pellagra. I desire it distinctly understood that I do not assert that the liver and the stomach secrete hormones, deficiency of which is essential for the production of pernicious anemia and pellagra. I merely advance the hypothesis of hepatic and gastric intrinsic factors in both diseases, with the hope that experimental and clinical investigations may be undertaken to prove or disprove that the liver and stomach secrete pernicious anemia-preventive factors.

Pathology of the liver and pancreas are almost constantly associated in sprue. Tom Brown, of Johns Hopkins, years ago advanced the theory that sprue results from a deficiency of the external secretions of the pancreas, and he found that the use of pancreatic extracts controlled the azotorrhea and steatorrhea in sprue—replacement therapy. It also has been known for years that the duodenum secretes an endocrine (secretin) which stimulates the external secretions of the pancreas. Is it not possible that sprue is essentially a disease of the duodenum and pancreas, and that when macrocytic anemia is associated with sprue it is due to associated liver dysfunction?

Assuming that chronic hepatitis may bear a relationship to pernicious anemia, pellagra, and sprue, what are the etiologic factors of the liver pathology? It would seem that gastro-intestinal infections of any kind may damage the liver, either by the absorption of exogenous, or endogenous toxins, or by metastatic infection carried directly from the blood of the stomach and intestines to the liver. Infection of the liver may result from the extension of a duodenitis through the common duct to the liver. This is shown by the frequent association of chronic cholecystitis and chronic hepatitis. In the case of sprue a pancreatitis, by destroying or inhibiting the function of the cells concerned with the external secretions of the pancreas, could result from the extension through the pancreatic duct to the pancreas of the infection responsible for duodenitis.

In other words, it would seem that in pernicious anemia, pellagra, and sprue, there is no specific organism responsible for any one of the three diseases, but it appears possible that any or all of the pathogenic organisms that may infect, or infest, the intestinal tract may cause liver pathology. This hypothesis fits in with the undoubted vitamin deficiency factor in pellagra for the reason that McCarrison has proved that intestinal infections follow the use of diets in which there is the lack of essential protective substances in food. It also explains how toxins such as ethyl alcohol and "pellagrazein," a phenylic alcohol, derived from spoiled corn, may cause pellagra.

There is evidence to show that the liver is involved in porphyrin metabolism and that hepatic damage may be followed by porphyrinemia and porphyrinuria. In the opinion of some, the skin lesions of pellagra may be explained by the photodynamic effect of porphyrinemia, resulting from the effects of endogenous or exogenous toxins in the liver, operative in pellagra but not in sprue or pernicious anemia. Proof of the presence of porphyrinemia in pellagra seems established, but the absence of porphyrin in the urine in sprue and pernicious anemia patients has not been proved.

*Is Liver Insufficiency the Essential Etiologic Factor in Pernicious Anemia?* In 1927 I submitted data on the etiology of pernicious anemia and outlined my views on the possible relationship of liver pathology to the development of that disease. It was suggested that the liver may secrete endocrines, the functions of which are to control erythrocytolysis by stimulation or repression of the reticuloendothelial system. A hemolytic hormone, a hemolysin, may stimulate the reticuloendothelial system to destroy red blood cells, and an antihemolytic hormone, and antihemolysin, may repress the activity of the blood-destroying apparatus. When the hemolytic and antihemolytic hormones are balanced, the normal level of 4,500,000 to 5,000,000 red blood cells per millimeter of blood is maintained. If there is a deficiency of the antihemolytic hormone, there is unrestrained hemolysis, and pernicious anemia results; and if there is a deficiency of the hemolytic endocrine, polycythemia follows. This hypothesis of the genesis of pernicious anemia fits in with the theory of William Hunter, who in 1888 suggested that excessive red blood destruction, rather than inadequacy of the blood-forming cells in the bone marrow, is the cause of pernicious anemia.

*Liver Hormones?* I have wondered for many years if the liver does not secrete a hormone which, working synergistically with the secretion of adrenin by the suprarenals, controls glycogenolysis. The pituitary secretes a number of hormones, which are synergistic with the internal secretions of the thyroid and suprarenal glands and are antagonistic to insulin. Perhaps the liver may secrete many hormones some of which have interrelations with the internal secretions of other organs involved in carbohydrate metabolism. Eosinophilic adenomas of the pituitary are so frequently found with polycythemia that it appears possible that this overworked "master" gland may secrete a hormone which has some relation to hematopoiesis or erythrocytolysis; and that there may be interrelations between the hormones of the pituitary and the liver which affect the number of erythrocytes.



in the blood. If an eosinophilic adenoma of the pituitary should secrete an excess of a hormone which acts synergistically with a hormone in the liver that represses reticulocytolysis, polycythemia would follow.

The type of clinician who demands pathologic proof before even considering any hypothesis will say that I am wandering in the realm of speculation when I suggest that the liver may secrete endocrines involved in maintaining stasis of the number of red blood cells circulating in the blood. There was a time when the idea that homeostasis of blood sugar was due to the balanced action of antagonistic hormones secreted by the islet cells of the pancreas and the medulla of the suprarenal glands was considered pure speculation; but Cannon and others have proved not only the existence of the hormones of the suprarenals and the pancreas but their antagonistic action to each other. Casimir Funk was speculating in 1911 when he suggested that deficiency of a factor in Vitamin B is the cause of pellagra; but his hypothesis has been proved. Cushing and others did a lot of speculating before they proved that the pituitary is the dominant endocrine organ of the body. I offer no apology for suggesting that the liver may secrete hormones, though I admit that I cannot offer proof that such is the case. I hope, however, that research workers who are prepared to make biologic laboratory investigations may prove, or disprove, (1) that liver insufficiency is the underlying factor in pernicious anemia, and (2) that hormones secreted by the liver may be factors in erythrocytolysis or hematopoiesis.

Identical pathologic changes in the liver are found in pernicious anemia and pellagra. It seems possible that liver insufficiency by inhibiting the secretion of an endocrine which controls erythrocytolysis or hematopoiesis may cause pernicious anemia, and that a deficiency of an intrinsic liver factor may prevent the utilization or the storage of nicotinic acid, the pellagra-preventive factor in Vitamin B.

*Gastric and Liver Pernicious Anemia-Preventive Factors.* Greenspon considers it possible that the liver secretes a hormone (endocrine) of which a gastric hormone is the precursor. Roger Morris and his associates defined the antianemia principle in the stomach as a hormone because they found that it is "dialyzable, exhaustible and that it withstands chemical treatment known to destroy enzymes." They have looked on this substance as "an internal secretion produced by the gastric mucosa."

McCollum cites Ungley, Castle and Hamm, Helmer and Fouts as having controverted Greenspon's theory and his findings; but they have not disproved Greenspon's "working hypothesis" of the etiology of pernicious anemia being a deficiency of hormones secreted by the stomach and liver.

Studies by Castle and Strauss, Roger Morris, Greenspon and others on what Castle called the "intrinsic factor," denominated by Roger Morris as an "internal secretion" of the stomach, and by Greenspon as a gastric "hormone," seem to prove a definite relation of impaired gastric function to pernicious anemia.

*The Interrelations of Vitamins and Hormones.* The interrelations of vitamins and endocrines is an intriguing subject which offers a fertile field for speculation, though there is evidence to show that vitamin deficiencies may cause dysfunction or pathology of the pituitary, thyroid, and adrenal glands. McCarrison,

two decades ago, called attention to the relationship of vitamin deficiency to endocrine disorders in relation to diseases of the intestines. McCarrison did not discuss pellagra and pernicious anemia as related to intestinal disease, but it seems justifiable to assume that the vitamin deficiency which causes hepatic insufficiency and adrenal dysfunction in intestinal infections may under proper conditions produce pellagra or pernicious anemia of which diarrhea is a frequent symptom. Naturally the question arises: Does liver insufficiency in pellagra and pernicious anemia result in one case in the hyposecretion of an endocrine, and in another prevent the utilization or storage of nicotinic acid in pellagra and a preventive vitamin factor in pernicious anemia? In other words, has it been definitely proved that nicotinic acid is a vitamin and not a hormone, and likewise is there evidence to show that the antipernicious anemia factor is a vitamin and not an endocrine?

*McLester on the Nature of Vitamins and Hormones.* J. S. McLester in the recently revised edition of his book "Nutrition and Diet in Health and Disease" expresses what is in the minds of many students of nutrition when he points out the difficulties of determining whether substances necessary for regulating nutrition are vitamins or hormones. In discussing the vitamins he says:

"They are included under the single generic term vitamin in part for the sake of convenience and in part because they are distinct from other food factors in the minuteness of the amounts required, but chiefly because they have in common a regulatory influence upon nutritive processes. Reasoning on this basis, however, one can find little justification for distinguishing between vitamins and hormones. In truth, the two have much in common, and it appears that there is good reason for grouping them together. The chief distinction (which does not hold in all instances) is that while hormones are formed within the body by the endocrine organs, vitamins are derived from the outside world through the medium of the food."

*Common Etiologic Factors in Pernicious Anemia, Pellagra, and Sprue?* My attention was focused on the possibility of a common etiologic factor in pernicious anemia, pellagra, and sprue by an article on that subject in 1925 by E. J. Wood, Jr., of Wilmington, North Carolina. At that time I was studying a case in which I had observed the transition from typical pellagra into the sprue syndrome and finally into typical pernicious anemia. This patient, who was known to have had achlorhydria when he had typical pellagra in 1916, several years after the dermatitis had cleared up, on leaving off the dilute hydrochloric acid, developed stomatitis and diarrhea, consisting of several large mushy stools a day, and several years later had severe macrocytic anemia.

*Report of Case of Pellagra, Sprue, and Pernicious Anemia.* This case showing that pellagra, sprue, and pernicious anemia may occur in the same person at different times came under my observation and was reported in 1926. In 1916 a pronounced pellagrin, male, was found to have stomatitis, achlorhydria, diarrhea, dermatitis, and mild mental depression, with red blood count of 3,800,000. He made a complete re-

covery following the use of 6 cc. (1½ grams) of dilute hydrochloric acid in a pint (500 cc.) of milk with meals and three hours after meals, combined with a high protein, rich vitamin diet. He has had no skin lesions of pellagra since 1916. He had sore mouth and a mushy diarrhea when he discontinued the diet and the dilute hydrochloric acid. Thus his symptoms at one time resembled sprue more than pellagra. In 1921 he returned to the clinic with no symptoms of pellagra, but presented a typical picture of pernicious anemia, i. e., lemon yellow skin, weakness, achylia, and a red blood count of 1,200,000; later count was 900,000. He was transfused 21 times from 1921 to 1926, usually with temporary benefit; he was kept on a diet, consisting largely of milk, meats, vegetables, and fruits, a high protein, rich vitamin diet. He gradually grew worse until it seemed the end was near, when in 1926, Minot and Murphy's work came out, liver was added to his diet. He liked liver and ate large quantities of it, and his red blood count rose in two months to 5,500,000, and he remained in excellent health until in 1936, when he was killed in a cyclone. He not only had the typical blood picture of pernicious anemia, but was cured by the liver diet. Several times both before and after he developed pernicious anemia he tried leaving off the dilute hydrochloric acid with the results that he would have the sprue syndrome, i. e., sore mouth and diarrhea, consisting of several large, light-colored, mushy stools a day.

In this case it appears that food deficiency, either in protein or vitamin content, could not have been the only factor in the etiology of the pellagra, sprue, or pernicious anemia. The patient was a successful farmer and merchant, who sold his plantation for \$35,000. He lived comfortably, and had an adequate diet. His wife and college-bred children were well nourished, and there were no other cases of pellagra in the family. He was living on a liberal, well-balanced, rich vitamin diet when he developed typical pernicious anemia in 1921. He continued this diet without improvement in his symptoms until in 1926 when the addition of liver to his diet brought his blood count from 900,000 to 5,500,000 in two months. It is evident that neither inadequate food intake nor vitamin deficiency could have been a factor in producing pernicious anemia in this case. The fact that even one individual had pellagra, sprue, and pernicious anemia in the order named, suggests the possibility of a common etiologic factor in the three diseases.

*Mallow's Cases of Pellagra and Pernicious Anemia.* Other clinicians have observed similarity in some of the manifestations of pellagra and pernicious anemia; and a few cases have been reported in which pellagrins developed typical Addisonian anemia.

Mallow pointed out in two articles that, in pellagra, symptoms of pernicious anemia may manifest themselves. He suggested that a study of such cases not only enlarges our clinical knowledge of pellagra but also contributes to the clearing up of the cause of pernicious anemia, which unfortunately is not yet known. Mallow reported two cases of macrocytic anemia in pellagrins, one with a red cell count of 730,000 and another with a count of 700,000. Liver therapy cured both cases.

*Alessandrini's Case with Symptoms of Pellagra, Pernicious Anemia, and Sprue.* Alessandrini, a cele-

brated Italian clinician, in 1934, reported the case of a woman, aged 40, who had symptoms of pellagra, pernicious anemia, and sprue. She had the characteristic pellagra syndrome, including red fissured tongue, mental depression, and the skin lesions on the backs of her hands. She had 3 or 4 foamy yellowish stools daily, microscopic examination of which showed large amounts of fatty acids and soap, and many muscle fibers. Examination of the blood showed macrocytic anemia; hemoglobin, 80 per cent; red blood cells, 3,200,000; leucocytes, 3,400; a few normoblasts, macrocytosis, and polychromatophilia. The woman died in an insane hospital four months later. No autopsy was made.

*Haden's Cases of Pellagra and Pernicious Anemia.* An important recent contribution to the literature on nutritional disorders is that by Russell L. Haden, of Cleveland, Ohio, in an article entitled "Multiple Specific Nutritional Deficiency Disease in the Adult." Haden discussed particularly that the "present state of our knowledge of the more important specific substances the lack of which leads to nutritional defects in the adult are (1) calcium, (2) iron, (3) vitamins A, B, B<sub>1</sub> (G) and C, and (4) the antipernicious anemia factor." He reported cases of "pernicious anemia and sprue, with low blood proteins"; "pellagra and pernicious anemia"; "pellagra, mild scurvy and hypochromic anemia"; and "iron deficiency anemia with subacute combined sclerosis of the cord."

It is interesting to note that in all of Haden's patients there was anachlorhydria or hypochlorhydria, and that in addition to a well-balanced diet, rich in vitamins, liver was used in those who improved.

Haden's report of his case of pellagra and pernicious anemia is interesting in that "with high vitamin feeding and liver extract intramuscularly" there was marked improvement in all the symptoms both of pellagra and pernicious anemia. Haden suggests: "It is possible that all this patient's difficulties followed the absence of some one factor supplied therapeutically by liver extract." Haden's report of his case of pellagra and pernicious anemia is as follows:

An unmarried woman, aged 60 years, had been losing weight for three months and had become increasingly weak and mentally dull. The dorsum of the hands showed marked wrinkling and a scaly dermatitis. The basal metabolic rate was minus 35 per cent. The blood examination showed red blood cells, 2,990,000; hemoglobin, 65 per cent (10 Gm.); volume index, 1.21; color index, 1.08; leucocytes, 10,100, with a normal differential count. The temperature ranged from normal to 102° F., but gradually returned to normal. With high vitamin feeding and liver extract intramuscularly, the edema disappeared, the mental processes became alert and the appearance was much brighter. The patient had the macrocytic anemia typical of pernicious anemia as well as the skin and mental changes seen in well developed pellagra. The picture is much like that produced by Miller and Rhoads in swine with a black tongue diet. It is possible that all this patient's difficulties followed the absence of some one factor supplied therapeutically by liver extract.

Of particular importance is Haden's statement that "multiple manifestations may be related to a single

deficiency." He cited the experimental work of Miller and Rhoads. They said:

"Using a diet which produces black tongue in dogs and which was considered by Goldberger to be deficient only in the pellagra-preventive factor, has produced in swine (1) an anemia usually macrocytic but sometimes microcytic, (2) ulcerative lesions of the oral mucous membranes, (3) gastric achlorhydria with the absence of the normal hematopoietic activity of the gastric secretion, (4) diarrhea and (5) motor weakness. With this diet which contains all mineral salts and known vitamins, they have thus produced symptoms suggestive of sprue, pellagra and pernicious anemia. The symptoms are prevented or cured by liver extracts, so these authors conclude that they are due to the lack of some unknown constituent contained in liver extract."

*Report of a Case of Pernicious Anemia and Sprue.*

In 1930 I treated a patient who had both pernicious anemia and sprue and in whom dramatic improvement followed the use of canned liver. A man, aged 50 years; height, 5 feet 9½ inches; weight, 107¾ pounds. He complained of "sore mouth, frequent stools, more in mornings and in evenings after supper, weakness and loss of weight." Physical examination was negative except that his skin had the lemon yellow tint of pernicious anemia. Physical examination was negative. Hemoglobin was 55 per cent; red blood count, 2,570,000; white blood count, 7,000. Wassermann was negative. Anachlorhydria. No blood or parasites were found in several specimens of feces. He was a charity patient and could not buy liver extracts, and living in the country he could not get fresh liver regularly. He was advised to try canned liver. He used Armour's "liver cheese spread" which retails at 10 cents a can, and wholesale at one dollar a dozen. His neighbors gave him their chicken livers, when they ate chicken.

In addition, a full diet, eliminating corn bread and cane sugar products, was prescribed. His neighbors also gave him milk, to which he added 6 cc. of dilute hydrochloric acid to each glass full, with meals and three hours after meals.

He returned for re-examination in four months when his hemoglobin was 75 per cent, and his red blood count 4,250,000 and white blood count 7,200. The stomatitis disappeared; his diarrhea had subsided and his weight had increased to 160 pounds. He felt well and was working every day on a little farm. A year later his hemoglobin was 85 per cent red blood count 4,500,000 and white blood count 8,600.

Three and a half years later, in 1937, he became careless about his diet and stopped eating the canned liver, when his sore mouth, diarrhea, weakness and anemia returned. At this time he had furuncles on the dorsal surfaces of his hands but the eruption bore no relation to the erythema of pellagra, and he gave no history of any pellagrous skin lesions. His hemoglobin had dropped to 38 per cent; his red blood count to 1,500,000 and white blood count to 5,000. He was advised to go back on canned liver and the dietary regimen he had followed in 1930.

In this case the use of dilute hydrochloric acid and an improved diet, containing canned liver and a liberal amount of milk, and eliminating corn bread, syrup and other cane sugar products, relieved the stomatitis and diarrhea of sprue and brought his

hemoglobin and red blood count to normal. Recrudescence of the symptoms of sprue followed when he discontinued the canned liver and returned to his former dietary habits, and his hemoglobin dropped to 38 per cent and red blood count to 1,500,000. This patient lives some distance from Birmingham and he has not been seen or heard from since his last visit when his low blood count proved the correctness of the diagnosis of pernicious anemia.

*Haden's Case of Sprue and Pernicious Anemia.* Haden, in 1936, reported a case of pernicious anemia and sprue. He said that "this patient had a macrocytic anemia due to a deficiency of the antipernicious anemia factor, and the low proteins, the leucocytosis, the diarrhea and the hypocalcemia of sprue. With intramuscular liver therapy the appetite returned, the edema began to disappear and before the patient left the hospital the bowel movements decreased to two or three a day with normally formed stools."

Edgar Hines, Jr., called attention to the sometimes difficult differential diagnosis between pellagra and sprue, and expressed the opinion that tropical sprue is not an infrequent disease in South Carolina and that no doubt cases of sprue have been incorrectly diagnosed as pellagra or pernicious anemia.

*Sydenstricker on the Relation of the Stomach and Liver to Pellagra and Pernicious Anemia.* Sydenstricker and Armstrong have had the idea of gastric and hepatic pathology as possible primary factors in the genesis of pellagra for some time. They discussed in their review of 440 cases of pellagra published in May, 1937, the importance of gastric and liver dysfunction in the etiology of pellagra.

Sydenstricker, predicating the existence of an intrinsic factor in the gastric juice as a factor in pellagra, seems to have shown that impaired function of the stomach, if not a *sine qua non* in the production of pellagra, is at least a factor. Sydenstricker, a clinician of unusual ability, with a flair for original investigations as shown by his work on sickle cell anemia, is impressed with the almost constant pathologic changes in the liver in pellagra—92 per cent in his series of 440 cases.

Added to this evidence of pathologic physiology of the liver and stomach in pellagra is the fact that liver and liver extracts cure pellagra. Deductions drawn from the original investigations of many clinicians led me to suggest that combined liver and gastric pathology, or pathologic physiology of both may be essential for the production of pellagra. Thus it appears that there is basis for the assumption of common etiologic factors in producing changes in the liver and stomach which produce in one case pernicious anemia and in another pellagra. This does not mean that I think pernicious anemia and pellagra are different manifestations of the same disease, though I do believe that they are allied nutritional diseases, having many symptoms in common; and possibly the same etiologic factors, with modifications, may act in the one case to cause pernicious anemia and in another pellagra.

Sydenstricker, in discussing the similar findings in cases of pellagra, pernicious anemia, and sprue, mentions the difficulty in occasional cases of making a differential diagnosis. He added: "More suggestive than apparent similarity in clinical manifestations is



the fact that liver extracts are curative in all three diseases." He also mentioned two of his patients "in whom typical Addisonian anemia developed after repeated attacks of pellagra."

Sydenstricker's originality in research was demonstrated by an experiment in which he showed that an extract made from the fatty liver of an untreated, uncomplicated fatal case of pellagra contained the antipernicious anemia fraction but not the pellagra-preventive factor as found in healthy livers. This led Sydenstricker to advance the "hypothesis that pellagra might result from intrinsic defect of the liver as well as from extrinsic deficiency."

Sydenstricker concludes as follows:

"Pellagra presents many phenomena analogous to pernicious anemia and sprue. In pellagra primary vitamin deficiency results, after varying periods of time, in gastric atrophy or dysfunction, in failure of liver storage of vitamin compound, in changes in the entire enteric absorptive mechanism, with diarrhea as a symptom."

Petrie and his associates (Act. med. Scandinav., 93:375, 1937) in discussing the gastrogenic etiology of pellagra suggest that "in view of the therapeutic efficacy of stomach preparations in pernicious anemia, pellagra and polyneuritis, these diseases may be of uniform etiology, that is, they represent a gastrogenic neurocutaneous syndrome."

*Possible Gastric Internal Secretion.* In 1927 I called attention to the fact that there is a known internal secretion of the duodenum, secretin, which when changed into prosecretin by the presence of dilute hydrochloric acid stimulates the secretion of trypsinogen and trypsin, amylase and steapsinogen and steapsin by the pancreas. At that time I also pointed out that secretin, or other internal secretion of the duodenum, is supposed to stimulate liver function.

It seems not impossible that the stomach may secrete an internal secretion which stimulates liver function. Reasoning a little further, may not the intrinsic gastric factor be an internal secretion which functions synergistically with liver endocrines?

*Hunter's Hemolytic Theory of Pernicious Anemia.* Murphy, in his recent book on "Pernicious Anemia" (W. B. Saunders Company, 1939), dismisses the role of infection in the gastro-intestinal tract as a factor in the production of pernicious anemia by saying: "There is little evidence available to support the theory of toxemia resulting from bacterial activity." He does not even mention the work of William Hunter, who in 1888 announced his theory of oral sepsis, the precursor of gastro-intestinal infections, as the primary cause of pernicious anemia. Others including myself believe that William Hunter went a long way toward predicating the correct theory of the etiology of pernicious anemia. Osler particularly was impressed with William Hunter's hypothesis of the genesis of pernicious anemia.

William Hunter found oral infections, particularly glossitis, and gastro-intestinal symptoms so constantly present in pernicious anemia that he believed pernicious anemia was a chronic infection due to streptococci and other septic organisms, affecting first the mouth and extending to the stomach and intestines. He believed that toxins formed in the gastro-intestinal tract were hemolytic, resulting in the destruction of

red blood cells faster than they could be manufactured by the blood-forming apparatus. Hunter accounted for the hyperplasia in the bone marrow as being due to a compensatory reticulocytosis. He also believed that the immature cells found in the circulation and in the bone marrow in pernicious anemia are due to the effort of the hematopoietic system to replace the loss of red blood cells destroyed by gastro-intestinal toxins.

Whipple, in 1922, opposed Hunter's theory of erythrocytolysis in pernicious anemia, expressing the opinion that it is due to "faulty blood construction and increased disintegration." Since that time, Peabody, Minot and Murphy and others whose investigations have been more in liver therapy than in etiology, accept Whipple's hypothesis.

Whether the "antipernicious anemia substance" in liver and liver extracts prevents erythrocytolysis or promotes reticulocytosis is not of great importance so far as controlling pernicious anemia but it seems possible that the "substance" in the liver may be a hormone.

*Intestinal Parasites in Pellagra, Sprue and Pernicious Anemia.* When pellagra was found to be endemic in the South, the campaign to eradicate hookworm was in progress. H. F. Harris, of Georgia, if not the first, was one of the first clinicians to diagnose uncinariasis in the United States. In 1901, two years before pellagra was found to be endemic in Alabama, H. F. Harris demonstrated in his clinic in the College of Physicians and Surgeons in Atlanta a case of hookworm, in which there were symptoms of pellagra. Sandwith reported that the first cases of pellagra recognized in Egypt were in patients who also had hookworm disease. Parrish, of Texas, found uncinaria in the feces of so many of his pellagra patients that he advanced the theory that pellagra was due to soil polluted with some parasite related to the uncinaria. Undoubtedly pellagra may be secondary to uncinariasis.

Several types of anemia were found in hookworm patients, some of which could not be diagnosed from pernicious anemia. The anemia in hookworm patients in Porto Rico was an outstanding feature. Colonel Bailey K. Ashford, of the Medical Department of the United States Army, was sent to Porto Rico to study hookworm anemia, and he found that sprue was a more difficult problem than hookworm disease among the inhabitants of that island. Ashford observed that the anemia of 5,000 hookworm patients on the Island of Porto Rico was cured by giving them thymol.

A much discussed question in the early days of the hookworm campaign was whether the parasites in fastening their hooklets to the intestinal mucosa cause minute hemorrhages, which in the aggregate caused the anemia, or whether they excreted a toxin which destroyed red blood cells. The toxin theory seemed more plausible. Severe macrocytic anemia occurs not infrequently in persons infested with the dibothriocephalus tapeworm. It is an interesting coincidence that Norway and Sweden, the only countries in northern Europe in which pellagra is endemic, also have a high rate of bothriocephalus tapeworm infestations associated with severe anemias.

Murphy cites Becker as having reported 18 cases of severe macrocytic anemia in patients infested with the bothriocephalus, and that treatment with liver

and liver extracts, without the expulsion of the worm, cured the anemia. This would suggest that liver insufficiency is the cause of the anemia in the bothriocephalus tapeworm. Liver and liver extract would seem to be replacement therapy in such cases.

The fact that a lipid substance obtained from segments of the bothriocephalus tapeworm will cause hemolysis suggests that in individuals infested with the short tapeworm the toxin is liberated in the intestinal tract and carried to the liver, there producing damage to the extent of causing liver insufficiency. The fact that the use of liver extract overcomes the anemia even when the worm has not been expelled further suggests that the liver insufficiency is the cause of anemia.

*Alcoholic Pellagra, Cirrhosis of the Liver, and Pernicious Anemia.* Alcoholism is a known cause of pellagra, in which pathologic changes in the stomach and liver may be assumed; and the fact that pernicious anemia is frequent in alcoholic cirrhosis of the liver, would suggest that liver insufficiency may occur in alcoholics who develop pellagra or pernicious anemia.

M. D. Van Duyn, 2nd, in an article on "Macrocytic Anemia in Disease of the Liver" reported a case of pernicious anemia in a patient who had cirrhosis of the liver. He made a careful study of the literature to determine whether or not in such cases "macrocytic anemia is secondary to, or independent of, hepatic cirrhosis; and if the presence of macrocytic anemia might not be an indication of disease of the liver?"

Van Duyn found a number of references in the literature to the association of macrocytic anemia with cirrhosis of the liver. In searching hospital records of the institution with which he is affiliated, he found that in 28 cases of cirrhosis of the liver, 5, or 18 per cent, also had macrocytic anemia.

William B. Murphy, in his recent very readable book on "Anemia in Practice and Pernicious Anemia" (W. B. Saunders Company, 1939), in discussing the cirrhosis of the liver associated with macrocytic anemia, seems to associate "liver damage to the storage of sufficient antipernicious anemia substance normally stored in the liver to hinder normal hematopoiesis." He adds: "The presence of some degree of cirrhosis of the liver is not uncommon in patients of the older age groups with pernicious anemia. In this group response to antipernicious anemia substance is likely to be slow because of the associated cirrhosis. Because of the slow and unsatisfactory response, one may be led to the conclusion that the cirrhosis is the primary disturbance rather than a complication of true pernicious anemia."

*Spies' Observations on Pellagra, Sprue and Pernicious Anemia.* Spies and Payne seem to have proved that pellagra and pernicious anemia are different diseases. They removed achylic gastric juice from the stomachs of two acute cases of pellagra on diets free from the pellagra-preventive factor. They incubated the gastric juice with beef and gave it to two pernicious anemia patients. A characteristic reticulocyte response showed the presence of Castle's intrinsic factor. The beef incubated with the gastric juice of pellagrins did not affect the course of the pellagra.

Williams and Spies say that "the peripheral neuritis

in patients with pernicious anemia cannot be distinguished pathologically from the peripheral neuritis associated with pellagra." They also state that "the peripheral neuritis of tropical and non-tropical sprue is clinically indistinguishable from that of beriberi, pellagra or pernicious anemia." I would add that while I believe pellagra, sprue and pernicious anemia are different diseases, it is an interesting fact that peripheral neuritis occurs in all three conditions.

Spies said: "It is my impression that pellagra, sprue and other similar conditions are probably closely related in that their development may be dependent on an inadequate food intake, or assimilation."

J. S. McLester in the last edition of his book on "Nutrition and Diet in Health and Disease" expressed the opinion that "sprue is a deficiency disease similar in nature to pernicious anemia and pellagra."

## CONCLUSIONS

1. Pellagra, pernicious anemia and sprue are distinct and separate disease entities.
2. The mouth and gastro-intestinal symptoms in pellagra, without skin lesions, pernicious anemia and sprue may be indistinguishable one from the other in cases in which there is macrocytic anemia.
3. The most effective treatment in pellagra, pernicious anemia and sprue is liver and liver extracts. Nicotinic acid is an ingredient of liver and liver extract.
4. Liver pathology, usually fatty degeneration, is an almost constant finding in pellagra and pernicious anemia and to a less extent in sprue. Atrophy of the stomach and intestines may be found in all three diseases. If cord changes are found in pellagra, pernicious anemia, or sprue, the lateral and posterior columns are involved.
5. Liver insufficiency appears to be a factor in the genesis of pellagra, pernicious anemia and sprue.
6. The hypothesis of liver endocrines as controlling erythrocytolysis is discussed.
7. Greenspon's and Roger Morris' suggestion of a gastric hormone as the intrinsic factor in preventing pernicious anemia is discussed. The interrelations and the similarity of vitamins and hormones are discussed.
8. Cases are reported, and collected, in which pellagra and pernicious anemia, sprue and pernicious anemia, pellagra, sprue and pernicious anemia existed in the same patients. This fact suggests common etiologic factors.
9. The frequency of intestinal parasites in anemic patients who have pellagra, pernicious anemia, or sprue is mentioned with the suggestion that intestinal toxemia and liver insufficiency may be etiologic factors in some cases.
10. Sydenstricker's views on the relation of the stomach and liver to pellagra and pernicious anemia are discussed.
11. The occurrence of pellagra in alcoholics, and the not infrequent complication of pernicious anemia in cirrhosis of the liver, suggests that liver pathology and, or, liver insufficiency, may be factors in alcoholic pellagra and pernicious anemia in patients who have cirrhosis of the liver.
12. Pellagra, pernicious anemia and sprue appear to be allied nutritional diseases.

## A Study of the Sphincter of Oddi in the Human and in the Dog\*

By

H. NECHELES, M.D., Ph.D.

and

D. D. KOZOLL, M.D.†

CHICAGO, ILLINOIS

AT the meeting of this society in 1938 we reported a study on the function of the gall bladder in the normal unanesthetized dog (1). In these experiments contraction and relaxation of the gall bladder alone was determined. Of a number of drugs tried then, adrenalin appeared to be the only one which contracted the gall bladder rather regularly and apparently emptied it. Now we want to report a study of the mechanism of the sphincter of Oddi in the human, and in the dog as far as they relate to our observations on the human subject. The pertinent literature has been reviewed and the detailed observations on the dog are reported in preceding papers on this subject (2-4).

**Methods:** Ten patients, 4 of them males and 6 females, were studied. All of them except one had had a cholecystectomy for gall stones and had a T-tube drain inserted in the common bile duct. Experiments were performed after the patients had recovered more or less completely from the operation; they drained clear bile through the T-tube, were afebrile, and were ready for removal of the T-tube drain. The one patient without stones was apparently suffering from cholangitis; at operation no stones or tumors were found to account for the obstructive jaundice. The resistance of the sphincter of Oddi was determined by a manometer recording on a kymograph, while a column of sterile .9% saline was perfused through the T-tube which was attached to the manometer by a side-arm connection (Fig. 1). This is similar to the method employed by Doubilet and Colp (5), Walters (6) and others. The animal experiments were performed on dogs anesthetized with pentobarbital sodium; gall bladder and duodenal motility and bile flow were recorded simultaneously, together with the resistance of the sphincter of Oddi as described above. The method has been reported in detail in another publication, and Fig. 2 illustrates the procedure (2).

**Results:**† 1. Drugs of the Adrenalin Group. Following our experience in the preliminary work mentioned above, compounds of the adrenalin group were tried. 0.5 cc. of adrenalin HCl were administered either intramuscularly or subcutaneously after a suitable control period, in which constant values for the resistance of the sphincter of Oddi had been obtained. Out of six tests on 5 patients, 4 showed a decrease of sphincteric resistance and 2 a considerable increase.

In 5 tests considerable fluctuations above and below the control level were observed. *Ephedrine sulfate*,  $\frac{3}{4}$  grain, intramuscularly, was followed by a considerable increase in sphincteric resistance in one test. *Epinine* 0.5 cc. subcutaneously or intramuscularly produced a very considerable increase in sphincteric resistance in 3 tests. This increased sphincteric resistance was followed by a considerable decrease of resistance far below the control level 40 minutes after administration of the drug. *Propadrine HCl*, 50 mg. intramuscularly was followed by considerable increase in sphincteric resistance in 2 tests. *Neosynephrin HCl*, 1 cc. per os, produced a very slight decrease in sphincteric resistance 30 minutes after administration.

We feel therefore that drugs of the adrenalin group cannot be employed by themselves for the emptying of the gall bladder because they may produce considerable contraction of the sphincter of Oddi although some of them had a biphasic effect with an impressive decrease of sphincteric resistance following the increase. This experience was confirmed by a large number of tests on dogs, in which the effects of the above drugs were found likewise to be inconsistent, although duodenal motility was often depressed for short intervals.

The next group of drugs employed were compounds usually considered as spasmolytic. *Atropine sulfate*, 1/100 of a grain, was administered subcutaneously to two patients. In both cases the resistance of the sphincter increased, particularly when effects of atropinization occurred, such as vertigo, sinking feeling, blurred vision, dry tongue, mydriasis. We feel that the latter observation may not be due so much to the atropine effect as the discomfort of the patient. In a number of occasions we have made the observation that discomfort and nausea from any other cause would have the same effect. Bergh (7) reported that in 10 patients, atropine had no consistent effect on the sphincter.

A suppository containing  $\frac{1}{2}$  grain of opium and  $\frac{1}{4}$  grain *belladonna* was administered to one patient. A considerable increase of sphincteric resistance occurred within 10 minutes, after which time the sphincter pressure fell below control levels. For the following two hours waves of contraction and relaxation of the sphincter were in evidence. *Papaverine HCl*, 50 and 30 mg. intramuscularly and subcutaneously respectively were administered to two patients. In one a prolonged increase in sphincteric resistance was observed lasting more than one hour. In another patient sphincteric resistance increased for the first ten minutes after injection and decreased to low levels 30 minutes later. A number of experiments on dogs confirmed the inconstant effects of papaverine. Similar variable effects of this drug on the human sphincter

\*From the Department of Gastro-Intestinal Research and from the Surgical Service of the Gall Bladder Group, Dr. Ralph B. Bettman, Michael Reese Hospital, Chicago, Illinois.

†Read at the meeting of the American Gastro-Enterological Association, Atlantic City, May 5th and 6th, 1941.

†Bernard Portis Research Fellow in Surgery.

†We are obliged to the following houses for a generous supply of drugs: F. Stearns & Co., neosynephrin and ephedrine; Sharp & Dohme, propadrine; Ciba Company, Trasentin; Merck & Co., Preparation No. 219; Winthrop Co., padutin, and Hoffman-La Roche, prostigmine.

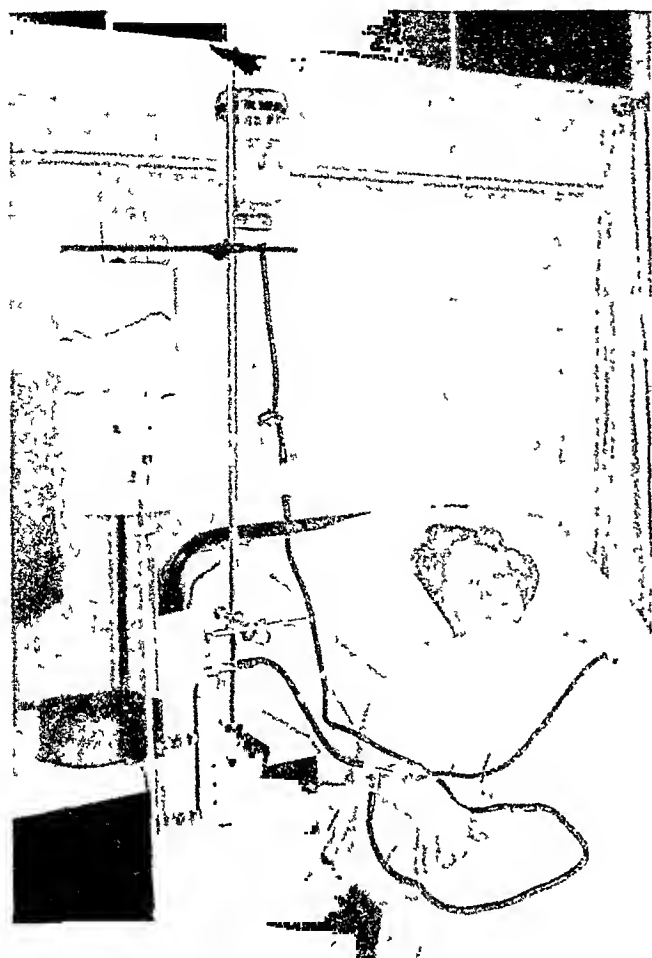


Fig. 1. Procedure Employed to Register the Resistance of the Sphincter of Oddi in the Human. The perfusion pressure of saline is registered by the oil-carbon-tetrachloride manometer on a kymograph.

have been reported by Colp and Doubilet and Walters, et al (5 and 6). *Morphine sulfate*  $\frac{1}{4}$  grain subcutaneously in one patient was followed by an increase of sphincteric resistance of 110 mm. of water at its maximum. The elevated sphincteric resistance lasted for 2 hours, and this was the only instance in which bile backed up into the side arm connection to the manometer. *Codeine phosphate* (Fig. 3 and 4),  $\frac{1}{2}$  grain and 1 grain was administered intramuscularly or subcutaneously to 4 patients. All of them had increased sphincteric resistance for periods of 1-2 hours similar to that following the administration of morphine. *Trasentin*, administered beforehand in one case, and atropine in another, decreased sphincteric spasm to codeine considerably. In one case illustrated in Fig. 3, *nitroglycerine* had to be given to relieve spastic distress; in the same patient *amyl nitrite* relieved the spasm induced by codeine for a shorter period of time than did nitroglycerine. The same results were obtained on dogs in which in addition spastic contraction of the duodenum was seen.

*Trasentin* and *Trasentin A*<sup>\*</sup> were administered to four patients in doses varying between 25 and 75 mg. subcutaneously or intramuscularly. *Trasentin* was followed by a decrease in sphincteric resistance while *Trasentin A* had only a slight or no effect. Experi-

\**Trasentin* is Diphenyl-acetyl-diethyl-n-minoethanol hydrochloride and *Trasentin A* is a derivative of the former, with one of the aromatic rings hydrogenated.

ments on dogs showed a similar effect on the sphincter and both drugs were followed by slight decrease of gall bladder tonus and a considerable decrease of duodenal tone and motility for short periods (8, 9).

*Cyverine*<sup>†</sup> (synthetic antispasmodic), 20 mg. per os were given to one patient. A moderate increase of sphincteric resistance was observed for ten minutes.

Preparation No. 219<sup>‡</sup>, 25 mg. intramuscularly in one patient was followed by a considerable decrease of sphincteric resistance 30 minutes after injection and the return to control values 45 minutes after injection. *Padutin* (or *Kallikrein*), a biological vaso-depressor preparation lowered sphincteric resistance first, then raised it, and 45 minutes after injection decreased it from a control value of 40 mm. of water pressure to 10 mm. In another experiment it had no effect. Likewise, inconstant results were obtained with this substance in a number of tests on dogs. *Amyl nitrite* was administered by inhalation to 4 patients; in one, a slight increase of sphincteric resistance, and in another one a considerable increase in sphincteric resistance occurred. In 3 patients to whom the drug was given when sphincteric resistance was greatly elevated following administration of morphine or codeine, a sharp transitory decrease of resistance occurred in both (Fig. 3). The relief of spasm was

<sup>†</sup>Methyl-bis-beta-cyclohexyl-ethyl-amino-HCl, Stearns  
<sup>‡</sup>Beta-Dimethyl-Amino- $\alpha$ -Phenyl- $\alpha$ -Ethyl-Propionic Acid Benzylester Hydrochloride Merck & Co

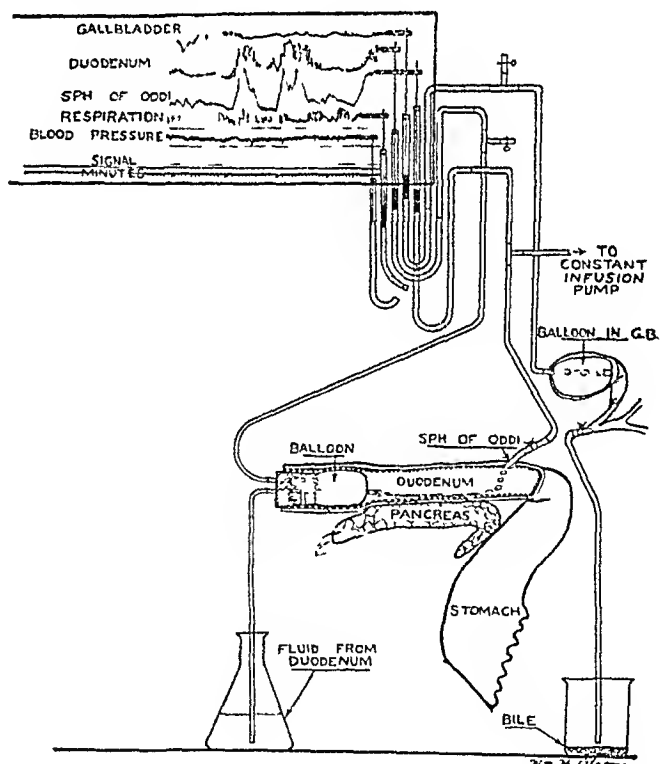


Fig. 2. Experimental Procedure Employed. Motility of gall bladder and duodenum recorded by balloon-oil manometer systems. Resistance of sphincter of Oddi to a constant perfusion with 0.9% saline recorded by another oil manometer. Respiration recorded by balloon placed between the liver and diaphragm, leading to a fourth oil manometer. Blood pressure recorded by mercury manometer. Glass cannula projecting beyond duodenal balloon for drainage of perfusion fluid entering through the sphincter of Oddi and for injecting solutions into the duodenum.

seldom more than 5 minutes duration. *Nitroglycerine*, 1/100 grain per os, administered after spasm producing agents, lowered sphincteric resistance regularly in 3 subjects, varying from intervals of 5 minutes to complete relief during a prolonged period of observation (Fig. 4).

Oil of *Peppermint* or Peppermint water (1:1000 solution) has been used as carminative for a long time and its effects have been described by Meyer, Necheles et al (10, 11). In 7 experiments the common duct was therefore perfused with *peppermint water*. In only two instances a considerable decrease of sphincteric

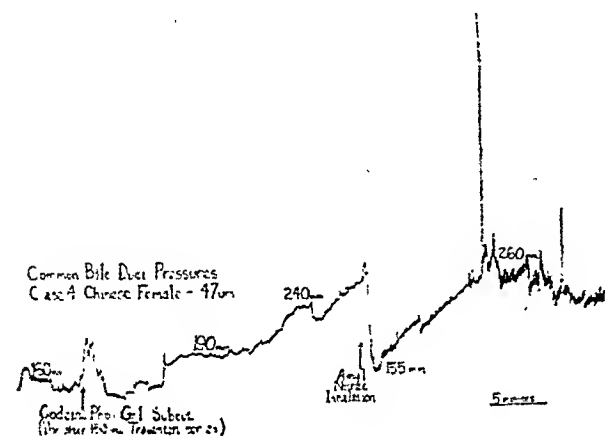


Fig. 3. Resistance of Sphincter of Oddi in the Human. Codeine following oral administration of an antispasmodic drug (Trasentin). The response to codeine is less than without previous medication of an antispasmodic and no pain was experienced by the patient; (compare with Fig. 4). Amyl nitrite lessened sphincter spasm only temporarily.

resistance was observed, while in five no effect was noted. One patient received one drop of peppermint oil on sugar by mouth. She was nauseated and sphincteric resistance increased for 5 minutes. It is believed that this increase was due to the nausea and not to specific causes.

In the case of the patient with cholangitis, bile flow was sluggish and amounted to less than 60 cc. in 24 hours before any tests were performed. Prolonged perfusion through the drain with normal saline resulted in the reestablishment of the flow of bile, so that 250 cc. of clear bile was recovered in the 24 hours following perfusion, and an improvement in the condition of this patient was noted. Judging from the previous mucoid and sediment content of the bile, it was believed that a mucous plug had been washed out by the saline from the proximal part of the common duct, into the duodenum. In another patient a small stone was lodged in the ampulla of the sphincter as shown by cholangiograms. Prolonged perfusion with saline dislodged this stone apparently into the duodenum, which was followed by striking improvement in the condition of this patient. Subsequent cholangiograms confirmed this. Following these experiences other solutions were tried with the idea that they might be more effective than saline. Peppermint water as described above was one of them and 1% sodium bicarbonate and N/50 HCl were also employed in six tests, but little or no effect of the latter solutions was observed.

Tincture of *valeriana*, citric acid and a watery solution of oil of *spearment* (1 in 1000) were also tried but had no or only slight effect on sphincteric resistance.

*Prostigmine-Methyl-Sulfate* .5 to 1 mg. was administered intramuscularly to 3 patients. In one of them a slight decrease of sphincteric resistance occurred. In the other two sphincteric resistance was increased for forty minutes and 2 hours respectively. In the latter subject waves of contraction and relaxation were noted during the two hour period. The same was observed in the animal experiments in which great and prolonged increases of sphincteric resistance and duodenal motility occurred without effect on the gall bladder.

In our observations in the acute experiments on dogs, we found that the instillation of *magnesium* or *sodium sulfate* into the duodenum was followed regularly by a marked and prolonged initial increase of duodenal and sphincter tonus and motility. Occasionally a lowering of sphincteric resistance below the control level followed the initial increase. This was of such a degree that it seemed hardly possible for the gall bladder to evacuate against such a resistance; besides, the gall bladder did not contract and even relaxed in one dog. Therefore, 60 cc. of 33% magnesium sulfate was instilled by duodenal tube into one patient. A mild contraction of the sphincter occurred lasting 3 minutes, which was followed by a slight drop in sphincter resistance lasting 5 minutes.

In a great number of experiments on dogs the intravenous injection of 0.9% saline solution or of 10 cc. of 20% NaCl solution was followed by vigorous contractions of the duodenum and by prolonged spastic contractions of the sphincter of Oddi. Since in post-operative therapy of human patients saline is given frequently, it seemed pertinent to repeat this on our patients. In one patient the intravenous injection of 900 cc. of normal saline solution was followed by a slight increase in tone and contractions of the sphincter, and following the intravenous injection of 200 cc. of 5% NaCl a slightly greater increase of sphincter tone and contractions was noted. In both cases the increase of sphincter tone was not as much as seen in the dogs, that is, not great enough to prevent the emptying of the contracting gall bladder; 500 cc. of 5% dextrose in distilled water intravenously diminished the tonus waves produced by the hypertonic saline.

A mixture of egg yolk and cream introduced into

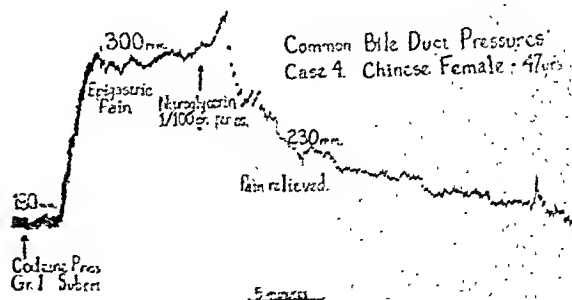


Fig. 4. (same patient as in Fig. 3). Administration of codeine was followed by sphincter spasm and pain. Nitroglycerine abolished spasm and relieved pain.



the duodenum of a patient increased sphincter tonus and contractions for 5 minutes and then tone and contractions fell to the control level. The same was found in dogs accompanied by a slight contraction of the gall bladder. The initial period, or "2 minute pause" described by Boyden (12) as preceding evacuation of the gall bladder which had been stimulated by a fat meal, may be explained by this observation.

In two of the patients we had the opportunity to observe sphincter resistance during the evacuation of a stool. A series of increased contractions of the sphincter, lasting about 5 minutes, seemed to accompany the passage of feces. From other observations on human subjects and on dogs we know that increase in intra-abdominal pressure, like coughing, sneezing, change of position and evacuation of bowels is followed by increased sphincter resistance.

In two patients we had the opportunity to observe the behavior of the sphincter before and during the intake of meals. Seven such observations were made. In 3 tests we were able to observe sphincteric tone (which was rather constant) during a prolonged period preceding the meal, but when the patient seemed to smell the food or see the nurse distributing it, sphincteric resistance became rather irregular. Waves of contraction and relaxation followed each other. In two instances sphincter tone increased and in 3 instances it decreased when the patient became aware of the meal. When the patient began to eat, sphincter tone increased in six instances. It seems plausible, therefore, to assume that there is a psychic effect of meals on the sphincter. Other observations on the subjects showed that nausea increased sphincter tone.

#### DISCUSSION

In the experiments on the human subjects sphincter tone only and its variations were measured. We do not know therefore what rôle duodenal motility may have played in our observations, but we were, however, able to make numerous observations on these relations in the dog. Likewise, we do not know, to what extent the sphincters of these choledochostomized patients can be considered to be normal.

During control periods on the sphincteric activity of the human and the dog, small tonus waves superimposed by individual contractions were noted. In many instances in the dog this was accompanied by contractions of the duodenum which often were of great intensity and subtetanic in type; often these powerful contractions did not affect the patency of the sphincter to the perfusion. That is, sphincter and duodenal tone were frequently independent of each other. The contractions in the duodenum of the dog were measured below the entrance of the ducts but the waves of contractions recorded by the kymograph travelled over the entire duodenum, and while we may have missed some, it is hardly plausible to assume that during the prolonged periods of observations none of these waves should have passed over the orifice of the sphincter of Oddi. The same independent activity of sphincter and duodenum was often observed during contractions of the duodenum produced by various drugs.

Egg yolk, cream and olive oil were followed by contraction of the gall bladder and increased tone and

contraction of the duodenum and sphincter in the dog, i.e. we did not see a reciprocal innervation of the gall bladder, duodenum and sphincter in the latter experiments. It is believed, however, that in the time interval between contraction and relaxation of the sphincter and duodenum the gall bladder might empty. The closest approach to a reciprocal mechanism of gall bladder evacuation was seen following the intravenous administration of a cholecystokin preparation<sup>\*</sup> in a prolonged tonic contraction of the gall bladder which outlasted the initial tonic and peristaltic contractions of sphincter and duodenum. Some time after the injections, sphincter and duodenum relaxed and the contracted gall bladder would have been able to evacuate bile into the duodenum. Moreover, an interval of several minutes elapses between the tonic contractions of the gall bladder and the response of the sphincter, during which effective evacuation of the gall bladder could have occurred.

In our experiments we had hoped to find a drug or combination of drugs that would contract the gall bladder and relax sphincter and duodenum. The only drug that consistently contracted the gall bladder, in addition to cholecystokin, was pilocarpine which, however, at the same time raised duodenal and sphincteric tonus to such a degree that emptying of the gall bladder did not seem possible. The response of pilocarpine is abolished by atropine or trasentin whereas that of cholecystokin was unaffected. Cholecystokin seems, in combination with an antispasmodic drug, to offer the best possibility to replace the gall bladder motor meal, if the former could be prepared for human use.

#### SUMMARY

Resistance of the sphincter of Oddi and its response to a number of substances was tested on 10 human subjects following operations and drainage of the common bile duct. Parallel experiments were carried out on dogs in which gall bladder and duodenal motility and sphincter resistance were measured simultaneously.

Drugs of the adrenalin group had variable effects on sphincter tone in the human and on the mechanism of gall bladder evacuation in the dog.

Symptoms of atropinization were followed by increased sphincter resistance in the human. The effects of papaverine were inconstant in man and dog. Codeine phosphate increased sphincter resistance greatly in the human and dog. Trasentin, nitroglycerine and amyl nitrite depressed sphincter tone, particularly when it was high following the administration of other drugs like codeine. Prostigmine usually increased sphincter tone considerably. Magnesium sulfate was followed by vigorous contractions of sphincter and duodenum in the dog but by only a slight increase of sphincter resistance in the human.

Lavage through the common duct drainage tube with saline solution was beneficial in 2 patients in whom obstruction of bile flow had occurred. In one of these patients a small stone lodged in the ampulla of Vater was apparently washed into the duodenum.

Coughing, nausea and passage of stools increased

<sup>\*</sup>Kindly prepared by Dr. D. Klein from the Wilson Laboratories, Chicago, Illinois.

sphincter resistance in the human. The sphincter of Oddi in the human seems to be subject to psychic effects, as the sight or odor of meals produced con-

siderable tonus waves of the sphincter. During the ingestion of the meal, sphincteric resistance increased in most patients.

## REFERENCES

1. Neeches, H.: A Study of Gall Bladder Function. *Am. J. Dig. Dis.*, 5:568, 1935.
2. Kozoll, D. D. and Neeches, H.: A Study of the Mechanics of Bile Flow. Simultaneous Observations on the Influence of the Gall Bladder, Sphincter of Oddi and the Duodenum Upon the Flow of Bile. I. Responses to Physiological Intravenous Solutions. In press, *S. G. O.*
3. Kozoll, D. D. and Neeches, H.: A Study of the Mechanics of Bile Flow. Simultaneous Observations on the Influence of the Gall Bladder, Sphincter of Oddi and the Duodenum Upon the Flow of Bile. II. Responses to Intraduodenal Solutions. In press, *S. G. O.*
4. Kozoll, D. D. and Neeches, H.: A Study of the Mechanics of Bile Flow. Simultaneous Observations on the Influence of the Gall Bladder, Sphincter of Oddi and the Duodenum Upon the Flow of Bile. III. Responses to Pharmacological Stimuli. In press, *S. G. O.*
5. Doubilet, H. and Colp, R.: Resistance of the Sphincter of Oddi in the Human. *S. G. O.*, 64:622, 1937.
6. Walters, W., McGowan, J. M., Butsch, W. L. and Knepper, P. A.: The Pathologic Physiology of the Common Bile Duct. *J. A. M. A.*, 109:1591, 1937.
7. Bergh, G. S.: The Effect of Atropine and Pilocarpine Upon the Sphincter of Oddi in Human Subjects. *Proc. Am. Pharm. Soc.*, 1941.
8. Neeches, H., Neuwelt, F., Steiner, N. and Motel, W. G.: Study of a New Spasmolytic Drug: Diphenylacetyldiethylaminocethanol Hydrochloride (Trasentin). *Am. J. Dig. Dis.*, VI, 39, March, 1939.
9. Spier, E., Neuwelt, F. and Neeches, H.: Clinical Study of a New Synthetic Spasmolytic Drug: Diphenylacetyldiethylaminocethanol. *Am. J. Dig. Dis.*, 6:387, Aug., 1939.
10. Meyer, J., Arcus, R., Neeches, H. and Sapoznik, H.: The Effect of Oil of Peppermint on the Emptying Time of the Stomach. *J. A. M. A.*, 104:20, 1935.
11. Meyer, J., Scheman, L. and Neeches, H.: Action of Oil of Peppermint on the Secretion and Motility of the Stomach in Man. *Arch. Int. Med.*, 66:99, 1935.
12. Boyden, E. A.: A Study of the Behavior of the Human Gall Bladder in Response to the Ingestion of Food. *Anat. Rec.*, 33:201, 1926.

## The Effect of Food Upon the Sphincter of Oddi in Human Subjects

By

GEORGE S. BERGH\*  
MINNEAPOLIS, MINNESOTA

MANY investigators have observed that the ingestion of food is followed by a flow of bile into the intestine. However, one may not infer from such an observation that food causes the sphincter to relax, since it is well known that certain food substances may cause both an increased secretion of bile and contraction of the gall bladder.

Since information concerning the response of the human sphincter to food is fragmentary, we have carried out a series of thirty-four experiments in an attempt to discover the effects of a fatty meal, a protein meal, and a carbohydrate meal.

### METHOD OF EXPERIMENTATION

These studies were carried out upon patients who previously had undergone cholecystectomy, choledochotomy and intubation of the common bile duct. As a preliminary procedure the anatomical status of the bile ducts was determined by cholangiographic examination.

Several weeks were allowed to intervene between the operation and the time of the experiments, and the studies were carried out after the patients had fasted for eight hours. The investigations caused the subjects no discomfort, and anesthesia was not required.

The apparatus, which was sterilized in the autoclave, consisted of an infusion flask connected by a rubber tube to the choledochostomy tube. A Murphy drip bulb was included in the system so that observations of flow could be made. The fluid injected was sterile, physiological salt solution.

By elevating or lowering the infusion flask the pressure within the duct system could be altered, and it could be read directly on a centimeter scale which was adjusted so that the zero point was at the estimated level of the common bile duct. In such a system,

when the duets were filled with the perfusion fluid, there was no flow as long as the sphincter resistance was equal to, or greater than, the pressure exerted by the column of solution. When the perfusion pressure exceeded the sphincter resistance there was a flow which could be detected through the Murphy drip

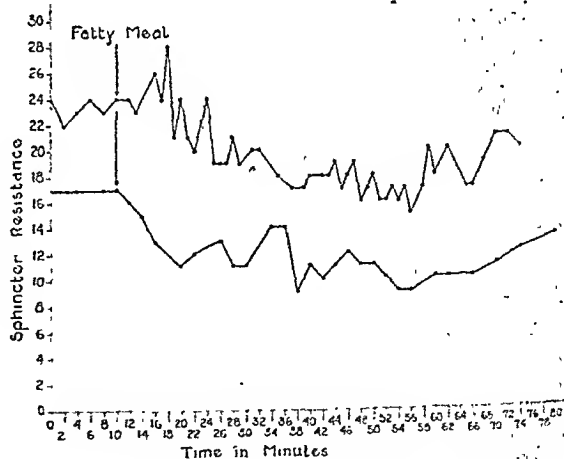


Fig. 1. Typical effect of a fatty meal upon the sphincter of Oddi (two patients). The lower curve shows relaxation of the sphincter without an initial contraction. The upper curve shows relaxation of the sphincter following an initial contraction. The sphincter resistance is recorded in terms of centimeters of water pressure.

bulb. The column of solution was adjusted to the exact level at which it was just supported without allowing any flow. The pressure then was read directly on the centimeter scale and was recorded as the sphincter resistance at that moment.

Before undertaking these studies, it was established that the ingestion of water alone did not influence the

\*From the Department of Surgery, University of Minnesota Medical School, Minneapolis, Minn.

sphincter tone (1). The effects of the different types of meals then were tested. Observations were continued for an average of seventy minutes after administration of the food, but were extended for more than three hours in some cases.

A fatty meal consisting of two raw egg yolks mixed in a glass of cream and flavored with sugar was given to fifteen patients. In four cases a meal of thirty to sixty cubic centimeters of olive oil was given. The oil was given by mouth in two cases and by duodenal tube in the others.

The protein meal, which was given to four patients, consisted of the whites of two eggs and two slices of lean, trimmed beef (each slice measuring about five centimeters in diameter).

The carbohydrate meal, which was given to eight patients consisted of two hundred cubic centimeters of sweetened fruit juice and two thin slices of un-



Fig. 2. The effect of a fatty meal upon the sphincter of Oddi. An initial contraction is followed by alternating periods of relaxation and contraction. Such changes in sphincter tone could influence the rate of gall bladder evacuation in response to a Boyden meal.

buttered white bread spread thickly with fruit jam. In three other cases the effect of intravenous administration of ten per cent glucose solution was studied.

### RESULTS

The egg yolk meal produced sphincter relaxation in fourteen of the fifteen experiments (Figs. 1-4). The relaxation began following an average delay of four minutes after ingestion of the meal. Previous to the relaxation in half of the cases there was a brief initial increase in the sphincter resistance (Fig. 1). This initial elevation of sphincter tone might account for the frequently occurring "two-minute pause" preceding the initial phase of gall bladder emptying as described by Boyden (3). The average maximum fall of sphincter resistance was seven centimeters of water pressure and occurred twenty-one minutes after the ingestion of the food (average), or seventeen minutes after the beginning of the relaxation. The average period between the maximum relaxation and the return to the original level of sphincter resistance was also seventeen minutes, making the total average

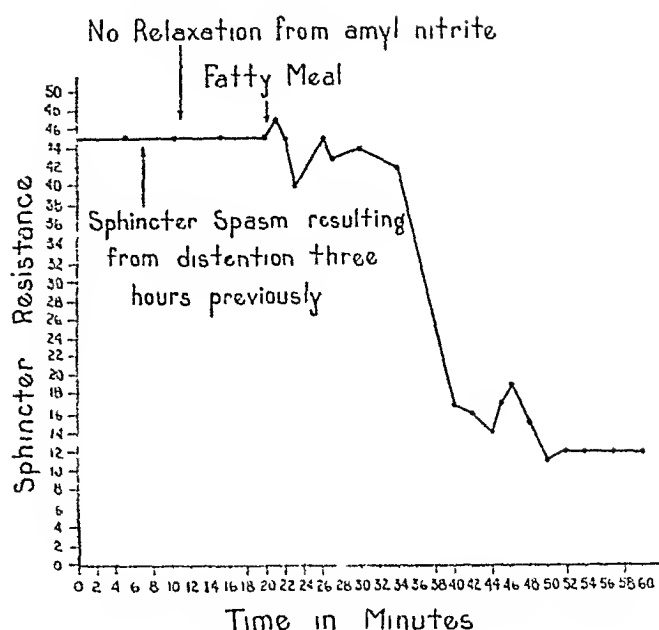


Fig. 3. The effect of a fatty meal upon a spastic sphincter. The spasm had been induced by sudden distention of the bile ducts three hours previously. Amyl nitrite failed to decrease the sphincter resistance, but a fatty meal produced prompt relaxation.

duration of the first phase of relaxation thirty-four minutes (Fig. 4). Subsequent fluctuations of sphincter resistance included relaxations and contractions of the muscle capable of determining later phases of gall bladder emptying (Fig. 2). Periods of relaxation sometimes were observed for as long as two or three hours after the meal.

In the four experiments in which olive oil was administered, there was very little decrease in the sphincter resistance in two cases and no relaxation in the others. The negative result might be due to the fact that fresh olive oil was used. Rost (9) has re-

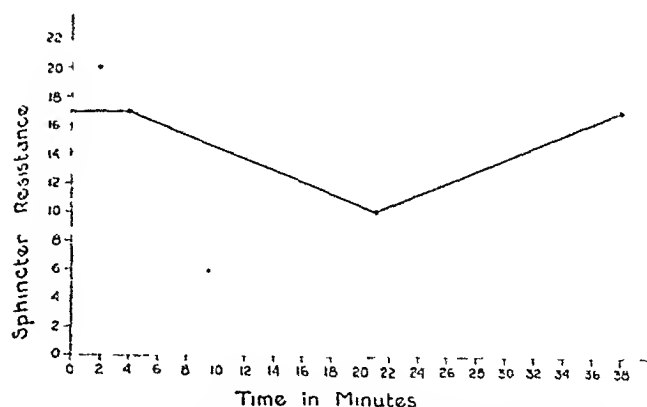


Fig. 4. Composite diagram illustrating the effect of a fatty meal upon the sphincter of Oddi. Relaxation began following an average delay of four minutes after ingestion of the meal. Previous to the relaxation in half of the cases there was a brief initial increase in the sphincter tone (represented by the broken line). The average maximum fall of sphincter resistance was seven centimeters of water pressure and occurred twenty-one minutes after the ingestion of the food. The average period between the maximum relaxation and the return to the original level of sphincter resistance was seventeen minutes, making the total average duration of the first phase of relaxation thirty-four minutes. Subsequent fluctuations are not recorded in the diagram.



ported that old olive oil produces a flow of bile in dogs, but that fresh oil is ineffective.

The protein meal produced sphincter relaxation only once in four experiments. In the other three cases there was no effect (Fig. 5).

Neither a carbohydrate meal (8 cases) nor ten per cent glucose solution administered intravenously (3 cases) had any significant effect upon the sphincter

intramural resistance. These observations may be correlated with the well-known facts concerning the effects of food upon the gall bladder. Cholecystographic studies have demonstrated that fats produce the greatest contraction of that organ, proteins rank next, and carbohydrates are practically ineffective in causing gall bladder evacuation.

Since the subjects upon which our experiments were performed had undergone cholecystectomy, it is apparent that the observed responses of the sphincter of Oddi to food were not dependent upon the presence of the gall bladder. Contraction of the gall bladder and relaxation of the sphincter following a fatty meal, therefore, appear to be independent reactions to the same stimulus.

### SUMMARY

Thirty-four experiments were carried out in order to study the effect of food upon the sphincter of Oddi in human subjects. A fatty meal consisting of egg yolks and cream produced relaxation of the sphincter, but fresh olive oil had little effect. Following a protein meal, relaxation occurred only once in four experiments. A carbohydrate meal did not produce a significant effect upon the sphincter resistance.

### REFERENCES

1. Bergh, G. S.: The Sphincter Mechanism of the Common Bile Duct in Human Subjects: Its Reaction to Certain Types of Stimulation. Doctor's thesis, University of Minnesota, 1940.
2. Best, R. R. and Hicken, N. F.: Nonoperative Management of Remaining Common Duct Stones. *J. A. M. A.*, 110:1257-1261, 1938.
3. Boyden, E. A.: An Analysis of the Reaction of the Human Gall Bladder to Food. *Anat. Rec.*, 40:147-191, 1923.

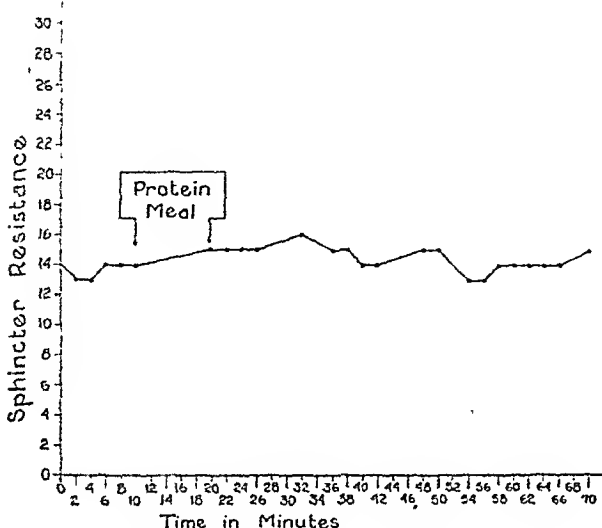


Fig. 5. Typical effect of a protein meal upon the sphincter of Oddi. In three of four experiments a protein meal did not produce a significant effect upon the sphincter resistance. In the fourth case a slight relaxation followed the meal.

(Fig. 6). In two cases momentary contractions of the sphincter occurred some time after the injection of glucose solution, but it is probable that these were spontaneous contractions rather than results of activity of the glucose (Fig. 6).

### DISCUSSION

Winkelstein and Aschner (11), Colc (5), McMaster and Elman (7, 8) and others have reported that food influences the sphincter to relax in dogs. In human subjects there is little information concerning the question. Carter (4) has stated that the external drainage of bile from a choledochostomy tube is decreased after a meal, indicating a relaxation of the sphincter. Walters (10) described one patient in whom biliary colic, produced by morphine, was relieved partially after eating. Best and Hicken (2) inferred from cholangiographic evidence that cream and olive oil produced relaxation of the muscle. Using direct measurements of sphincter resistance, Doubilet and Colp (6) found that, in one case, a full meal did not influence the sphincter; in another patient a meal of soup, two eggs and ice cream had no effect; and, in a third case, clear chicken soup produced slight relaxation.

The results of our experiments indicate that a fatty meal of egg yolks and cream produces relaxation of the sphincter of Oddi, but fresh olive oil is without significant effect. A protein meal occasionally produces relaxation. Neither a carbohydrate meal nor ten per cent glucose solution intravenously affects the

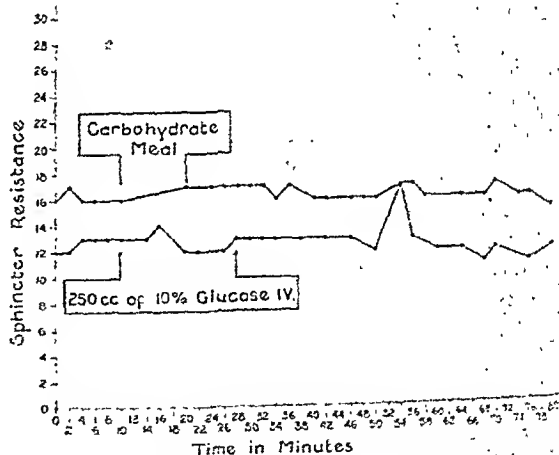


Fig. 6. Typical effect of carbohydrates upon the sphincter of Oddi (two cases). Neither a carbohydrate meal nor ten per cent glucose solution administered intravenously had any significant effect upon the sphincter. The momentary contraction occurring twenty-six minutes after discontinuing the administration of glucose (in the lower curve) probably was a spontaneous contraction not related to the effect of the glucose.

4. Carter, R. F.: When to Remove the Drainage Tube in Common Bile Duct Drainage. *S. G. O.*, 63:163-165, 1936.
5. Cole, W. H.: Relation of Gastric Content to the Physiology of the Common Duct Sphincter. *Am. J. Physiol.*, 72:39-42, 1925.
6. Doubilet, H. and Colp, R.: Resistance of the Sphincter of Oddi in the Human. *S. G. O.*, 64:622-633, 1937.
7. Elman, R. and McMaster, P. D.: The Physiological Variations in Resistance to Bile Flow to the Intestine. *J. Exper. Med.*, 44:121, 1926.
8. McMaster, P. D. and Elman, R.: On the Expulsion of Bile by the Gall Bladder and a Reciprocal Relationship with the Sphincter Activity. *J. Exper. Med.*, 44:173, 1926.

9. Ro-t, F.: Die funktionelle Bedeutung der Gallenblase. Experimentelle und anatomische Untersuchungen nach Cholecystektomie. *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 26:710-770, 1913.
10. Walters, W.: The Pathological Physiology of Stone in the Common Bile Duct. *S. G. O.*, 63:417-424, 1936.
11. Winkelstein, A. and Asehner, P. W.: The Pressure Factors in the Biliary-duct System of the Dog. *Am. J. Med. Sci.*, 168:812-819, 1924.

### DISCUSSION

DR. WILLIAM O. ABBOTT (Philadelphia): Mr. President, I want to congratulate the authors on two extremely interesting papers. They raise one important question, however. By referring to the sphincter of Oddi as the mechanism controlling bile flow they imply that the contractions of the duodenal wall itself are not the controlling mechanism. Since contraction of the duodenum mediates to some extent the emptying of the stomach, it becomes important for us to know, I believe, whether one can obtain clear-cut contractions of the sphincter of Oddi in the sense of inhibited bile flow, without simultaneous contractions of the duodenum. Thus, the question as to whether it is the sphincter of Oddi or the duodenum that is controlling bile flow becomes one not only of academic but of clinical interest, and I should appreciate the opinion of the authors in this regard.

DR. H. NECHELES (Chicago, Ill.): I was very glad that Dr. Bergh's presentation followed mine. I was not able to report all our experiments. We had similar results with egg yolk and cream as Dr. Bergh. We observed the "two-minute" pause too, but in our case it was five minutes. We also observed that nausea produced by any cause would be followed by a contraction of the sphincter of Oddi. Any increase in intra-abdominal pressure, like sneezing, coughing, or movements of the patient, were followed by increases of sphincteric resistance. Bowel

movements were followed by increased sphincteric resistance, but we do not know, of course, whether this is due to increased intra-abdominal pressure or to a reflex from the rectum.

In answer to Dr. Abbott's question about the effect of these substances on the emptying time of the stomach, I believe we have eliminated this factor by giving the substances as Boyden docs, i.e. by intraduodenal instillation.

Of course, we know that oils and fats will stay in the stomach longer and that in the beginning only small quantities will get into the intestine, but a small quantity of oil or egg yolks which leaves the stomach will cause inhibition from the duodenum and that small quantity may have some effect on the gall bladder and sphincter.

We were surprised that in the dogs olive oil had very little effect on the gall bladder, although instilled into the duodenum very slowly. The olive oil did not produce much contraction of the sphincter, while egg yolk and cream or a mixture of both did.

DR. GEORGE S. BERGH (Minneapolis, Minn.) (closing the discussion): I would like to add one point concerning the effect of the duodenal musculature upon the control of the flow of bile. I think that it is considerably less important in human subjects than in animals. Dr. Boyden particularly has shown that the structure of the choledochoduodenal junction differs in man and in animals, and that the window through which the bile duct enters the intestine is so arranged that one would not expect the duodenal musculature to play an important part in regulating the flow of bile in man. Furthermore, Dr. Layne and I have demonstrated an independent activity of the human sphincter of Oddi.

## Porphyria in the Aged\*

By

HENRY A. RAFSKY, M.D., F.A.C.P.

and

BERNARD NEWMAN, B.S., Ch.E.

NEW YORK, NEW YORK

IN an earlier paper (1) we reported our findings regarding Vitamin C retention and excretion in so-called "normal" aged men and women, namely, that in a group of 25 such subjects, who received comparatively large doses of cevitamic acid, only 8 per cent showed a more or less constant saturation point; the remainder, 92 per cent, retained comparatively large amounts of cevitamic acid. This investigation was thought of interest, as despite the voluminous literature on the clinical significance of Vitamin C deficiency in adults, scant attention had been paid to this condition in aged individuals.

Vitamin studies in "normal" aged individuals are being continued and one of these has been investigation of the status of these subjects with regard to nicotinic acid saturation. There is no direct test for assaying nicotinic acid levels in body fluids. However, in studies of human pellagra porphyria has been observed to be constant in the untreated pellagrin and to disappear following adequate nicotinic acid therapy. The determination of the presence or absence of por-

phyrins in the urine therefore was deemed suitable to indicate, although most indirectly, the status of our subjects with regard to nicotinic acid saturation. Beckh, Ellinger and Spies (2) point out that there is no specific test for porphyria. Similar pigments which give a positive reaction in the tests now applied may appear after X-ray sickness, gastro-intestinal disorders, febrile states, hepatic disturbances, hyperthyroidism, diabetes mellitus, and the ingestion of certain drugs (3). However, the test becomes negative after treatment with yeast, liver, and nicotinic acid or its amide in these disorders just as it does in pellagra similarly treated.

In view of these circumstances, the test for porphyria described by Beckh, Ellinger and Spies (2) and applied by Spies, Sasaki and Cross (4) in their study of the relationship of porphyria and human pellagra, was utilized as an appropriate qualitative index of the nicotinic acid saturation in our group of aged individuals. None was suffering from any active disease and all were housed in the "Home" division of the institution, were ambulatory, and were on the usual diet given to this type of resident. It was believed therefore that a positive test for porphyria

\*From the Hospital and Home of the Daughters of Jacob, New York, New York.  
Submitted May 15, 1941.

might be a reflection of nicotinic acid deficiency as in pellagrins since none of the disorders causing the production of porphyrins or similar pigments was present in the case of any member of the group.

The group studied included 100 subjects: 35 men and 65 women. Their ages ranged from 63 to 104 years. Considering the environmental factors, it can be said that every member was as "normal" as any individual past 63 years of age. Urine specimens were taken from the first morning voiding—usually at 5:30 a. m.—and were tested for porphyrine by the method described by Beckh, Ellinger and Spies (2) as follows:

"Detection of Ether-Soluble Red Pigment in Urine. To 10 cc. of urine in a separatory funnel, add about 0.2 cc. of glacial acetic acid. The resulting mixture should have a pH of approximately 4.0. Then add 15 to 20 cc. of ether. The mixture is shaken for several minutes to insure complete extraction of any ether-soluble pigments present. After standing for a few minutes, the water and ether fractions separate. The LOWER

(according to decade of life) follows closely the normal probability.

| No of Subjects | Age Group | Positive Tests  |
|----------------|-----------|-----------------|
| 9              | 60 - 69   | 4 cases or 44%  |
| 52             | 70 - 79   | 20 cases or 38% |
| 25             | 80 - 89   | 17 cases or 68% |
| 4              | 90 -      | 2 cases or 50%  |

3. The frequency distribution of positive tests for porphyrinuria follows very nearly the normal probability curve.

4. The frequency distribution of negative tests for porphyrinuria follows very nearly the normal probability curve. (The age-frequency distribution of the positive and negative tests for porphyrinuria is graphically portrayed in Fig. 1).

5. These data may be transferred and applied to the general population of the same group age in a

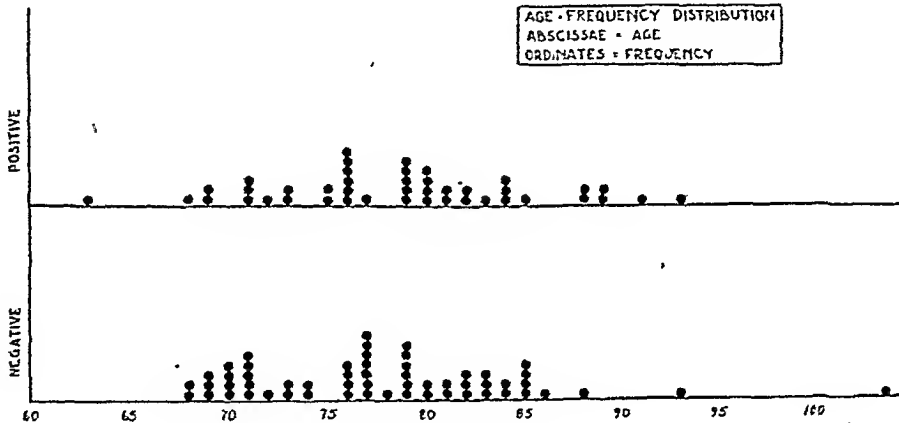


Fig. 1

AQUEOUS layer is drained out and discarded. The ether fraction remaining in the funnel is washed twice by shaking with 10 to 15 cc. of distilled water, each time discarding the lower aqueous layer. To the washed ether extract, add 3 cc. of 25% HCl. The mixture is shaken and transferred to a test tube. In specimens of urines which contain ether-soluble red pigments (porphyrin-like pigments), a pink-to-purple color develops on the addition of the hydrochloric acid. When this occurs, the test is said to be positive."

In our application of this method, an interval of 15 minutes was allowed for the development of a pink to purple color. If this occurred within the specified time the test was considered positive.

The age, sex, clinical status, and result of the test for porphyrinuria in the case of each member of the group are listed in Table I. Analysis of this table shows the following:

1. The mean of age group used is circa 79 years.
2. The incidence of porphyrinuria in subgroups

similar environment since there was very little variation in the percentage of positive tests as the number of cases increased: for the first 50 cases, 41%; for 75 cases, 45%, and for 100 cases, 43%.

It may be reasoned that the large percentage of positive tests in these aged individuals may be due to frank or occult hepatic dysfunction secondary to impairment of the cardiovascular system attendant upon senile or involutional degenerative changes in this system. However, impaired liver function associated with cardiovascular pathology is usually one of the manifestations of chronic passive congestion following decompensation. All of our subjects were ambulatory and regardless of the degenerative cardiovascular changes were in perfect compensation. The incidence of positive urinary tests in subjects who had no cardiovascular involvement of clinical significance and of negative tests in subjects with marked degenerative cardiovascular changes—although in compensation—is confirmatory evidence that cardiovascular disease of itself does not cause porphyrinuria. In cases of chronic passive congestion of the liver due to cardiovascular decompensation, tests for

porphyrinuria may be positive according to Beckh, Ellinger and Spies (2) and Dobriner and Rhoads (3).

This study is being continued, quantitative urinary determinations are being made in the cases in which the test for porphyrinuria is positive, nicotinic acid is being administered, and the effect of this treatment upon urinary excretion of the porphyrins is being determined. The findings obtained from continuation of the study will be reported at a later date.

### CONCLUSIONS

In a series of one hundred so-called normal aged individuals, 43% had porphyrinuria. This is consid-

ered to be due to nicotinic acid deficiency as the other conditions which may be responsible for porphyrinuria or the production of pigments leading to a positive test for porphyrinuria, were not present.

### REFERENCES

1. Rafsky, H. A. and Newman, H.: Vitamin C Studies in the Aged. *Am. J. Med. Sci.*, 201:749, May, 1941.
2. Beckh, W., Ellinger, P. and Spies, T. D.: Porphyrinuria in Pellagra. *Quart. J. Med.*, 6:305, July, 1937.
3. Dobriner, K. and Rhoads, C. P.: The Porphyrins in Health and Disease. *Physiol. Rev.*, 20:416, 1940.
4. Spies, T. D., Sasaki, Y. and Cross, E.: A Note on the Relationship of Porphyrinuria to Human Pellagra. *South. Med. J.*, 31:483, 1938.
5. Turner, W. J.: A Theory of Porphyrinogenesis. *J. Clin. and Lab. Med.*, 26:323, 1910.

## Lymphosarcoma Causing Obstruction at the Duodenojejunal Angle: Report of Case

By

HENDRIK J. SVIEN, M.D.\*

and

ANDREW B. RIVERS, M.D.†

ROCHESTER, MINNESOTA

**I**N the field of gastro-enterology, the small bowel is relatively unexplored. The tendency still is to consider abdominal symptom complexes which are not explainable on the basis of lesions of the stomach, duodenum, colon or lower portion of the small bowel as likely to be caused by functional disease. No doubt, many lesions which involve the small bowel remain undetected unless they extend progressively and eventually block the viscus.

The most common lesion which produces obstruction high in the small bowel is duodenal ulcer. Other causes of duodenal obstruction may be divided into intrinsic and extrinsic types. The most important intrinsic causes usually are assumed to be congenital narrowing, foreign bodies, pressure by diverticula, tumors, either benign or malignant, or inflammatory disease invading the intestinal wall. Potential extrinsic causes include bands of adhesions, either congenital or acquired, enlargement or ptosis of the right kidney, aneurysms of the abdominal aorta, which may press the duodenum against the mesenteric vessels, anomalies or diseases of the pancreas or extension of inflammatory disease from the gall bladder. It is rather surprising that diseases which invade the gall bladder cause mechanical disturbance in the duodenum so infrequently. A diseased gall bladder, even though it has enlarged tremendously, rarely produces obstruction of the small bowel. Occasionally, a large gall stone passes into the duodenum through a cholecystoduodenal fistula and causes obstruction of that organ. Occasionally, duodenal obstruction is caused by pressure of lymph nodes which surround the intestine. At times, prolapse of the duodenum or pressure behind it by pushing the intestine against the mesenteric vessels may cause either intermittent or chronic interference with the normal emptying of the duodenum.

In 1934, one of us (Rivers) and Thiessen reviewed thirty-five cases in which obstruction occurred in the duodenum below the ulcer bearing portion or in the

first 5 or 6 cm. of jejunum proximal to the segment usually utilized in performing gastro-enterostomy. In fifteen of the twenty-six cases in which obstruction of the middle portion of the duodenum was present, the obstruction was caused by carcinoma of the pancreas, in three by primary carcinoma of the duodenum, in three by lesions involving the duodenum, gall bladder or pancreas in which the exact location of the original lesion could not be determined, in two by inflammatory lymph nodes, probably tuberculous, in one by an accessory pancreas, in one by pancreatitis and in one by a benign tumor of the duodenum. Of the group in which obstruction was at the duodenojejunal angle, it was due in one case to a diffuse inflammatory process of undetermined etiology, in one to malignant infiltration of the wall of the bowel and in another to twisted mesentery secondary to an anatomic abnormality. In the third group of cases, those in which the obstruction was in the upper 5 or 6 cm. of jejunum, it was caused by post-operative adhesions in one case, in one by jejunal ulcer, in one by tuberculosis, in one by congenital bands and in two by inflammatory processes arising in the jejunal wall; in one of the last two cases a syphilitic lesion involved the jejunal wall.

We are reporting a case of intestinal obstruction at the duodenojejunal angle caused by a relatively rare lesion which produced obstruction in a manner still more rare.

### REPORT OF CASE

A man, thirty-eight years of age, registered at the Mayo Clinic on August 30, 1940. The history before 1936 was not significant except for appendectomy performed in 1929; in the course of convalescence, an abscess of the right lung had developed, but complete recovery had ensued. The patient then had been in good health until December, 1936, at which time a dull, aching pain with a cramplike quality had begun in the right middle portion of the abdomen. This pain which usually occurred after breakfast and disappeared after lunch was associated with heartburn or sour stomach. In January, 1937, he began to vomit once a day at variable times after meals. The vomiting had continued in spite of the daily use of antispasmodic drugs. In November, 1937, the home physician

\*Fellow in Surgery, Mayo Foundation.

†Division of Medicine, Mayo Clinic, Rochester, Minn.

Submitted May 15, 1941.

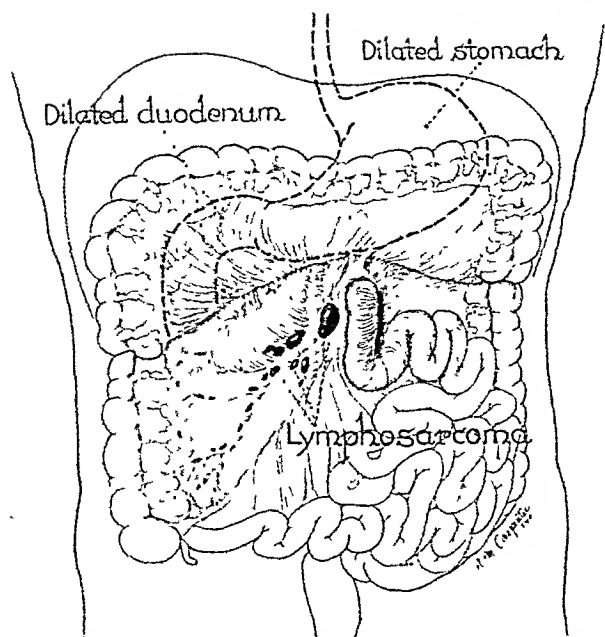


Fig. 1. Location of enlarged mesenteric nodes producing intermittent intestinal obstruction at duodenojejunal angle.

found on roentgenologic examination that his stomach was dilated. In January, 1938, diarrhea developed and he passed as many as twelve stools daily; this condition had persisted for four months. The patient also stated that he had noticed undigested particles of food in the stools. In May, 1938, he had stopped taking all medicine. The vomiting and diarrhea had ceased, he had gained 20 pounds (9 kg.) and had felt well until March, 1940. At that time he had noticed loss of appetite, weight and strength, and diarrhea had recurred for a week. Subsequent to this, he had begun to have epigastric pain, associated with excessive borborygmus. The epigastric pain had no relation to meals and was not relieved by ingestion of food. He had experienced some nausea, eructation of gas and heartburn during the month previous to registration at the clinic.

Results of physical examination were essentially negative, except for mild distention of the upper portion of the abdomen and a small, firm, freely movable mass about 3 cm. in diameter, which was palpable in the right portion of the abdomen at the level of the umbilicus.

The value for hemoglobin was 11.4 gm. per 100 cc. of blood. Erythrocytes numbered 4,620,000 and leukocytes 12,400, for each cubic millimeter of blood. A blood smear revealed nothing of diagnostic value. Results of urinalysis and of the flocculation test were negative. Gastric analysis revealed a total acidity of 36 and free hydrochloric acid, 26 (Töpfer's method), and gastric retention of 550 cc. Examination of stools was negative for parasites, ova and excessive fat. Result of the skin tuberculin test was negative. Proctoscopic examination revealed only external and internal hemorrhoids. On roentgenologic examination, the thorax, gall bladder, stomach, colon and terminal portion of the ileum disclosed nothing abnormal; findings in the first and second portions of the duodenum were indeterminate. An excretory urogram indicated that both kidneys were normal grossly.

While in the hospital for observation, the patient vomited copiously on numerous occasions and on one occasion the vomitus contained coffee ground material. Gastric lavage revealed retention of 800 to 2,000 cc. Exploratory operation revealed a large, dilated stomach and a slightly dilated duodenum. Multiple rounded masses were found in the mesentery of the proximal portion of

the jejunum at the duodenojejunal angle (Fig. 1). The bowel at this point was thick walled and somewhat dilated. The lesion was too extensive to permit resection and accordingly, gastrojejunostomy was carried out. Several mesenteric lymph nodes were removed for biopsy (Figs. 2, 3 and 4). The pathologist reported lymphosarcoma.

After dismissal from the hospital, following an uneventful recovery, the patient received eleven treatments with Roentgen-rays to the epigastric region. When last heard from, he stated that he was relieved of symptoms and that he was gaining weight.

#### COMMENT

Invasion of the mesentery or intestine by lymphosarcoma is relatively uncommon. In 1919, Graves reviewed from the literature 249 cases and added three of his own. In 1932, Ullman and Abeshouse added 125 cases to those reviewed previously by Graves and added one of their own, making a total of 378. Since then, additional cases have been reported by Charach, Grilli, Leveuf and Godard, Khalfen and Abgarov and Benjamin and Christopher.

The studies of Graves and of Ullman and Abeshouse indicate that lymphosarcoma occurs twice as frequently in the small intestine as in the large; in the small intestine, the ileum is the most common site of the disease, the jejunum is involved more frequently than the duodenum, and the lesions may be multiple. In most cases, the predominant symptoms are those of acute or chronic intestinal obstruction and they are more frequently accompanied by dilatation than by stenosis of the intestine. Lymphosarcoma may involve the intestine as an annular or polypoid growth; in some instances, stenosis of the bowel is due to marked involvement of the mesenteric lymph nodes, which tend to aid in compression of the lumen of the bowel. Males have a greater predisposition to the disease than females, a ratio of 5:2. The disease is found most frequently in the first, third and fourth decades of life; the average age incidence is 33.2 years.

Geschickter found that sarcoma constituted 3 per cent of malignant growths, of which lymphosarcoma was the major form. Hartman, in reviewing cases of

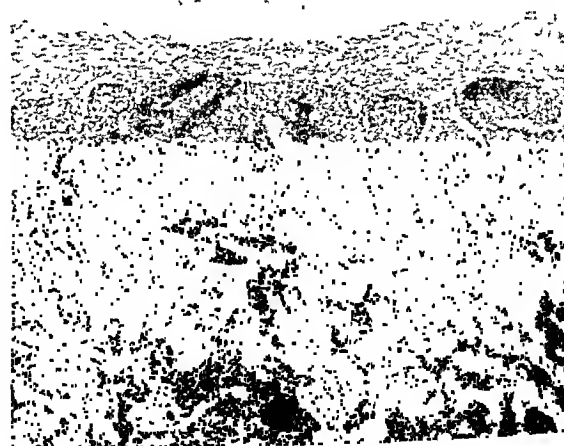


Fig. 2. Inflammatory lymph node. Well-formed follicles surrounded by relatively clear zones or sinuses can be seen. The follicles do not encroach on the capsule. Clearly defined pale zones and hyperplasia of reticular cells can also be seen (x45).

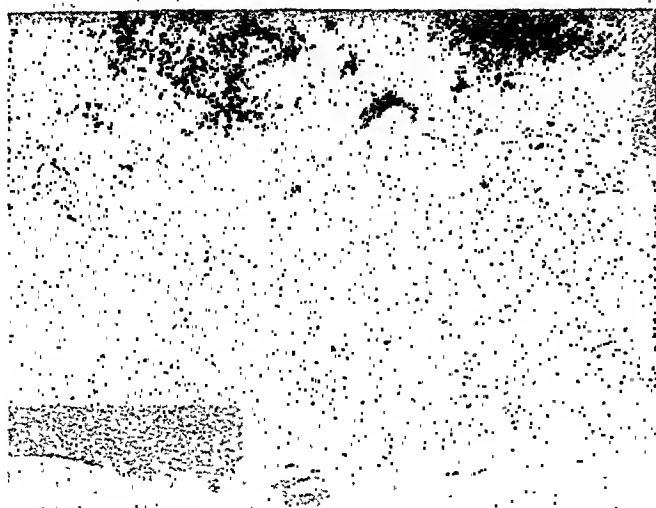


Fig. 3. Lymphosarcoma. As compared with Fig. 1, the follicles have disappeared and the lymphoid tissue has fused with the capsule. Sinuses are absent and no line of demarcation between lymphoid and reticular elements can be seen (x30).

malignancy of the small bowel encountered at the Mayo Clinic, found seventy carcinomas and twenty-five sarcomas, a ratio of 2.8:1. Usher recently reviewed the records in fifty cases of lymphosarcoma in which the small bowel, colon and rectum were involved. In reviewing the symptoms and findings in these cases; he reported discovery of a palpable tumor in 86 per cent. The detection of superficial lymph nodes as an aid in the diagnosis cannot be depended on. Usher noted that in only four of the cases in which the lesions involved the small bowel did any evidence indicate involvement of peripheral lymph nodes. At exploratory operation, however, evidence of metastasis was found in the mesenteric lymph nodes in about 68 per cent of cases; intussusception was present in 12 per cent. The complaint of most of these patients was cramping pain and most of them gave evidence of considerable loss in weight. The discovery of blood in the stool was rather rare in the cases in which the jejunum, ileum, cecum and colon were involved, but was common in cases in which the rectum was involved.

The case which we have reported illustrates the importance of careful evaluation of symptoms in the absence of a demonstrable lesion in the stomach or duodenum. Roentgenologic evidence of persistent dilatation of the duodenum and retention of large amounts of residue of bile tinged material suggesting a block below the ampulla made it obvious that somewhere in the upper portion of the small bowel there must be either an intrinsic or an extrinsic lesion invading the viscus. Pain arising from disturbances involving the upper portion of the small bowel usually is situated

about the umbilicus. In our case the pain was in all probability attributable to intermittent distention of the duodenal loops caused by peristaltic rushes in the attempt to overcome the periodic mechanical obstruction. After the duodenal contents had been forced through the partially blocked portion, circular muscle spasm of the intestinal wall disappeared, resulting in dissipation of pain.

The possibility of lesions invading the small bowel must always be remembered in attempting to evaluate symptoms which are localized to the umbilical region. In such cases when lesions involving the stomach, duodenum, colon and lower portion of the ileum cannot be demonstrated the entire small bowel should be searched carefully by roentgenologic investigation or at exploratory operation. If this is done, many lesions doubtless will be discovered which are producing the distress that at present is attributed to functional disease.

#### REFERENCES

1. Benjamin, E. L. and Christopher, Frederick: Primary Lymphosarcoma of the Small Intestine. *Am. J. Clin. Path.*, 10:408-413, June, 1940.
2. Charache, Herman: Primary Lymphosarcoma of Intestine. *Am. J. Surg.*, 27:171-173, Jan., 1935.
3. Geschickter, C. F.: Quoted by Usher, F. C. (11).
4. Graves, Stuart: Primary Lymphoblastoma of the Intestine. Report of Three Cases, One with Apparent Recovery Following Operation. A Plan for Logical Classification of Tumors. *J. M. Research*, 40:415-431, Sept., 1919.
5. Grilli, A.: Forme rare del linfosarcoma primitivo del tenue. *Ann. di radiol. e fis. med.*, 10:57-68, Feb., 1936.
6. Hartman, H. R.: Quoted by Usher, F. C. (11).
7. Khalfen, S. S. and Abgarov, V. J.: Lymphosarcoma of the Small Intestine. *Klin. med.*, 15:619-620, 1937.
8. Leveuf, J. A. and Godard, H.: Les sarcomes cavitaires de l'intestin grêle chez l'enfant. *Ann. d'anat. path.*, 13:1067-1084, Dec., 1936.
9. Rivers, A. B. and Thiesse, N. W.: Obstruction of the Upper Portion of the Small Intestine; a Clinical Study. *Am. J. Dig. Dis. and Nutrit.*, 1:92-96, April, 1934.
10. Ullman, Alfred and Abeshouse, B. S.: Lymphosarcoma of the Small and Large Intestines. *Ann. Surg.*, 95:878-915, June, 1932.
11. Usher, F. C.: Lymphosarcoma of the Intestines. Thesis, Graduate School of the University of Minnesota, 1940.

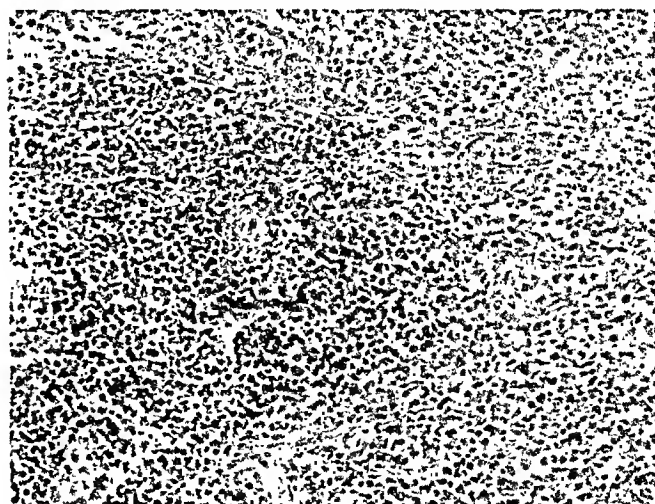


Fig. 4. Area of Fig. 2 under high magnification. Complete disorganization of normal architecture and the presence of hyperchromatic malignant cells (lymphoblasts) can be noted (x200).

## Editorial

### SOME OF GREAT BRITAIN'S NUTRITIONAL PROBLEMS DURING THIS WAR

ON November 10, 1941, in Rochester, Minnesota, Sir John Boyd Orr, Advisor to the Minister of Nutrition in Great Britain, Director of Rowett Research Institute, Aberdeen, Director of the Imperial

Bureau of Animal Nutrition, and Research Lecturer in the Physiology of Nutrition, University of Aberdeen, gave a most interesting talk on some of the problems of nutrition in the British Isles during this war.

He remarked first on the fact that in the eighteenth



century the men of Northern England and Southern Scotland, who then lived in the country and had plenty of whole wheat grain, milk, eggs and vegetables, were big, powerful, energetic men who made the best infantry soldiers in Europe. At the time of the Boer War, around 1900, the military authorities were greatly disturbed to find that a large percentage of the recruits from this district were short, frail weaklings who could not be used as soldiers. The generals insisted that a commission be appointed to find out why this was, and the most probable explanation found was that many of the people had moved off the land and had gone into the slums of big cities. There their eating habits had changed, and they were depending too largely on white flour and sugar. The same sort of change took place in other big industrial cities of England and in the East End of London.

The military authorities were concerned again in 1914 and in 1940, when so many of the men who came up for the draft had to be rejected because of small stature and a poor state of nutrition. Today, Sir John says, a tremendous change has taken place in the attitude of Britain's rulers toward this problem. For the first time in the history of the British Government the cabinet ministers have turned to physicians and experts in nutrition and have said, "Here, you know what's wrong and you know what to do. Tell us what to do to remedy the situation, and so far as is in our power we will do it." As a result, great efforts are being made now to secure from abroad those foods which, will take up the least space in the holds of the few ships that are available, and second, will give the maximum of calories and the maximum protection from deficiency diseases. The ships are now bringing wheat, fats, dried milk, dried eggs and dried fruits, and in England they are digging up lawns and parks and are planting potatoes, which give the greatest number of calories per acre.

Sir John said that he doubts if ever again the people of England will allow the children in the slums to go without enough food, and especially the food that will insure proper growth and development. This has seemed such a foolish thing to do, especially when the elevators of Canada, the United States and the Argentine were bursting with unsalable grain.

It was interesting to hear Sir John say frankly that although it seems certain that there must be about us

innumerable cases of mild dietary deficiency states of various kinds, their recognition will probably always be difficult because, as every experienced clinician knows, the unscrambling of the symptoms that are due to nervousness or constitutional inadequacy and those that are due to a lack of vitamins must often be impossible. And as Sir John said, the wise and experienced physician will never be satisfied with the argument that a nervous woman must have been suffering with a borderline avitaminosis because she got better when given a daily dose of several vitamins. Many such a one gets well only to relapse later, in spite of the fact that she is still taking her vitamins. It seems probable that in the future the borderline states will be recognized and identified largely with the help of new laboratory tests which will show whether or not the person's bodily stock of vitamins really is low.

But even when this is accomplished, the problem will remain of determining what are the safe limits of normal for the intake of each vitamin, and at what low level symptoms will appear. Sir John felt that these standards are now being determined with a fair degree of accuracy, and he was delighted to see that the figures that are being chosen in this country by the Committee of which Dr. Wilder is Chairman, correspond closely to those that are being adopted in Great Britain.

The essential point, as Sir John said, is that there can be no question that hundreds of thousands of the children of the poor are undernourished in almost every way. As most workers in the field of avitaminoses have pointed out, such undernourished persons may not show decided signs of any one recognized deficiency disease, but when they are given more food, some milk, butter, cod liver oil, eggs, vegetables and fruit, they blossom out, not only physically but mentally. They promptly show greater vivacity, intelligence, and joy in life, and they often end up by topping their parents by 4 or 5 inches.

A most thoughtful article on the new spirit of co-operation now developing between governing bodies and scientific men is to be found in the November 21, 1941, issue of "Science." It is from the pen of Dr. A. V. Hill. All men interested in the advancement of science should read it.

W. C. A.

## Abstracts of Current Literature

FRANKLIN HOLLANDER, Associate Editor in Charge of Abstracts, New York, N. Y.

ALBERT CORNELL, New York, N. Y.  
MAURICE FELDMAN, Baltimore, Md.  
CHARLES A. FLOOD, New York, N. Y.  
M. H. F. FRIEDMAN, Philadelphia, Pa.  
J. DUFFY HANCOCK, Louisville, Ky.  
THOMAS A. JOHNSON, Philadelphia, Pa.  
ALLEN A. JONES, Buffalo, N. Y.  
N. W. JONES, Portland, Ore.  
HENRY H. LERNER, Boston, Mass.  
PHILLIP LEVITSKY, Montreal, Can.

JESSIE LOVE, Louisville, Ky.  
FRANZ J. LUST, New York, N. Y.  
IRA A. MANVILLE, Portland, Ore.  
ARTHUR E. MEYER, Brooklyn, N. Y.  
FRANCIS MURPHY, Milwaukee, Wis.  
H. NECHELES, Chicago, Ill.  
FRANK NEUWELT, Gary, Indiana  
SAM OVERSTREET, Louisville, Ky.  
J. F. PESSEL, Trenton, N. J.  
DAVID J. SANDWEISS, Detroit, Mich.

RUDOLPH SCHINDLER, Chicago, Ill.  
MICHAEL SHUTKIN, Milwaukee, Wis.  
VIRGIL E. SIMPSON, Louisville, Ky.  
H. J. SIMS, Denver, Colo.  
HENRY TUMEN, Philadelphia, Pa.  
ROBERT TURELL, New York, N. Y.  
EDGAR WAYBURN, San Francisco, Calif.  
JOHN WILLARD, Philadelphia, Pa.  
C. WILMER WIRTS, Philadelphia, Pa.

### CLINICAL MEDICINE

#### STOMACH

BERRY, LEONIDAS H.: *Right Side Gastroscopic Technique in Situs Inversus Viscerum and in Visualization of "Blind Spots."* *The Review of Gastro-Enterology*, 8:267, July-Aug., 1941.

The right side, or dextro-lateral position, is probably the most satisfactory for the gastroscopic examination of cases of situs inversus viscerum. A sort of mirror image

of the normal stomach is seen in these patients in this position, and there is complete disappearance of the posterior wall "blind spot" and partial disappearance of the antral lesser curvature "blind spot." Twenty-four patients with normal placed stomach were examined in the dextro-lateral position; twenty-three showed improved visualization in at least one area. In six cases pathologic lesions were found in this position but were not visible in the standard position.—C. Wilmer Wirts.



## Gall Bladder Dyspepsia\*

By

ROLLIN H. MOSER, M.D., BERNARD D. ROSENAK, M.D.

and

ROBERT J. HASTERLIK, M.D.

INDIANAPOLIS, INDIANA

"JUDD, whose extensive surgical experience with cholecystic disease enabled him to speak with authority, once stated that no one actually knew what constituted chronic cholecystitis either from the standpoint of clinical symptoms or from that of pathological findings" (1). On the other hand, for many years able clinicians have spoken of chronic gall bladder disease as the most common cause of dyspepsia. By dyspepsia we mean that group of symptoms, the commonest of which are described by the patient as a "sense of fullness in the epigastrium," "bloating," "gas," "sour stomach," "belching," "water brash," and intolerance to certain foods. We do not include pain or colic.

Is there a dyspepsia due to gall bladder disease? If so, why is the incidence of post-cholecystectomy symptoms so high in spite of the fact that definite pathology including stones may have been present? Most clinicians are agreed that the removal of the non-calculous gall bladder for dyspeptic symptoms is very likely to be followed by unsatisfactory results. There is, however, no such general agreement when the stone-bearing gall bladder is considered. Bissgard and Dornberger (2) in a study of 836 cases of gall bladder disease state that the number of cures was much higher in those patients who had colic than in the non-colic dyspeptic group and that the commonest cause of failure was error in diagnosis and attributing symptoms to gall bladder disease because of X-ray evidence. Street (3) believes that the failure of surgery is often due to associated pathology in the liver, pancreas, or bile ducts but is more often due to the fact that the pre-operative symptoms were not caused by biliary tract disease and that emphasis should be placed on pain rather than vague digestive symptoms in the selection of cases for operation. Moore (4) in a study of 50 cholecystectomized patients concluded that much of the disappointment in the results of surgery could be avoided if every patient presenting symptoms simulating gall bladder disease and lacking a history of colic were first placed on medical therapy and only on its failure, operated upon. Palmer (5) has stated, "it is possible, that these so-called gall bladder dyspepsias do not differ materially from those seen in patients not afflicted with cholecystitis or other forms of organic disease," and "that this so-called 'gall bladder dyspepsia' is in reality quite independent of the gall bladder."

The frequent return of patients to our clinic because of failure to gain relief from dyspeptic symptoms following cholecystectomy prompted a study of

this problem. The subjects of this investigation were seen in the Gastro-Intestinal Clinic of the Indianapolis City Hospital and were the type of patient usually encountered in a large charity institution. All had stone-bearing gall bladders which had been removed. Every patient was repeatedly seen by all of us. We emphasize this last statement because we believe that the usual mailed questionnaire type of follow-up study is likely to result in gross errors. It is not accurate to speak statistically of the percentage of cases having recurrent symptoms as there is no doubt that more patients with symptoms return than those who gained relief. Control groups consisted of patients who had colic only and were relieved, those having colic and/or dyspepsia with relief, and a group of patients whose dyspepsia was due to the so-called irritable colon.

A very careful history of each patient was taken on several occasions. The following examinations beside a complete physical examination were made: blood

TABLE I  
*Classification of cases studied*

|                |   |
|----------------|---|
| Group 1.       | Forty-nine patients having persistent dyspepsia after cholecystectomy for acute or chronic cholecystitis with stones. |
| Control Groups |   |
| Group 2.       | Patients completely relieved by cholecystectomy for colic only.   |
| Group 3.       | Patients completely relieved of both colic and dyspepsia by cholecystectomy.  |
| Group 4.       | Patients with irritable colon syndrome presenting symptoms similar to "gall bladder dyspepsia."                       |

count, urinalysis, Kahn and Kline, gastric analysis, duodenal drainage, blood cholesterol, serum bilirubin, intravenous modification of the hippuric acid test, gastroscopy, X-ray examination of the stomach and colon, and a pathologic study of the removed gall bladder.

It was hoped by this investigation to learn something of the nature of the dyspepsia which occurs in gall bladder disease as well as to investigate the dyspeptic phase of the so-called post-cholecystectomy syndrome. The group of patients which received most of our attention consisted of forty-nine individuals who had cholecystectomies for calculous gall bladder.

A detailed statement of the pathological findings in each case is not presented at this time. A comparison of pre- and post-operative symptoms with the histopathology of the gall bladder shows no correlation between the degree of pathologic change and the expectancy of an operative cure. In the group of patients presenting post-operative dyspepsia many instances of severe cholecystitis with stones were encountered. This fact immediately suggests that there is little or no re-

\*From the Gastro-Intestinal Clinic of the Indianapolis City Hospital; aided by a Grant from the Lilly Endowment.  
Read at the Annual Meeting of the American Gastro-Enterological Association, Atlantic City, N. J., May 6, 1941.

lationship between the dyspepsia in gall bladder disease and the degree of cholecystic pathology.

Table II shows the various causes of persistent dyspepsia after removal of the gall bladder. There were thirty-three patients whose symptoms were considered to be due to irritable colons (Table II, Part 1). The diagnosis of this condition was based on a repeated history of irregular bowel habits, frequent use of cathartics, presence of mucus in the stool in many instances, and abdominal pain and tenderness. The only examination which was frequently positive was

TABLE II. PART 1

*Analysis of causes of post-cholecystectomy dyspepsia*

| Sub-group A. 33 Cases of Irritable Colon                  | Associated Conditions                      |
|---|--|
| Diagnosis based on:                                       | Reduced sugar tolerance ... 12 cases       |
| 1. Irregular bowel habits                                 | Arteriosclerosis ..... 3 "                 |
| 2. Cathartic habit  | Ventral hernia ..... 3 "                   |
| 3. Abdominal pain and tenderness                          | Achlorhydria ..... 4 "                     |
| 4. Barium enema (spasm)                                   | Periduodenal adhesions ... 1 case          |
| 5. Symptoms relieved by smooth diet, antispasmodics, etc. | Atrophic gastritis ..... 1 "               |
|   | Superficial gastritis ..... 1 "            |
|   | Biliary dyskinesia ..... 1 "               |
|   | Pancreatitis ..... 1 "                     |
|   | Pernicious anemia ..... 1 "                |
|   | Aerophagia ..... 1 "                       |
|   | Instances of associated pathology ..... 29 |

TABLE II. PART 2

| Sub-group B. Unclassified Dyspepsia and Food Intolerance 10 cases                   | Associated Conditions                     |
|---|---|
| Diagnosis based on:   | Menopause ..... 1 case                    |
| 1. Gas, bloating, fullness, belching, pyrosis, regurgitation, etc.                  | Achlorhydria ..... 1 "                    |
| 2. Above symptoms caused by fats, beans, cabbage, onions, fried foods, apples, etc. | Latent syphilis ..... 1 "                 |
| 3. No disturbance of bowel function   | Congenital hemolytic anemia ..... 1 "     |
| 4. No X-ray evidence of gastrointestinal pathology                                  | Rheumatic heart disease 1 "               |
| 5. Symptoms improved on bile salts (Biltron) and not improved on bowel management   | Reduced sugar tol. .... 3 cases           |
|   | Instances of associated pathology ..... 9 |

TABLE II. PART 3

| Sub-group C. Diverticulitis of the Colon 2 cases | Associated Conditions          |
|--|--------------------------------|
| Diagnosis based on:                              | Pancreatitis ..... 1 case      |
| Sub-group D. Superficial Gastritis 1 case        | Ventral hernia ..... 1 "       |
| Diagnosis based on:                              | Psychoneurosis ..... 1 "       |
| 1. pronounced gastroscopic evidence              | Hypochlorhydria ..... 1 case   |
| Sub-group E. Pancreatitis 1 case                 | Reduced sugar tolerance 1 case |
| Diagnosis based on:                              |                                |
| 1. Epigastric pain in addition to dyspepsia      |                                |
| 2. X-ray signs of pancreatic pathology           |                                |
| 3. Elevated serum lipase                         |                                |
| 4. Operative findings                            |                                |

the barium enema which revealed spasticity in seven of nineteen examinations (Table III). Sigmoidoscopic examination usually revealed no significant abnormalities. The response to treatment consisting primarily of a bland diet, antispasmodics, and bland, bulk-producing drugs\* was considered of value in establishing this diagnosis.

The fact that there were twenty-nine instances of associated abnormalities in the thirty-three irritable colon cases was regarded as highly significant. In most cases these secondary conditions were thought to contribute to the post-operative symptoms. Table III shows the results of the routine tests and examinations in this group of patients. The results of the barium enema examinations have been mentioned. Most of the other studies were of negative importance, only helping to eliminate gastric or biliary tract pathology as possible causes of persistent symptoms. Certain inconsistencies appeared for which a satisfactory explanation is lacking. We refer particularly to the high incidence of reduced glucose toler-

TABLE III

*Laboratory and X-ray studies on 33 group I patients with irritable colons*

|   |   |
|---|---|
| A. X-ray of Stomach and Duodenum<br>26 Examinations<br>1 Periduodenal adhesions<br>25 Normal    | F. Gastric Analysis<br>24 Examinations<br>7 Achlorhydria<br>2 Hypochlorhydria<br>5 Hyperchlorhydria<br>10 Normal      |
| B. X-ray of Colon<br>19 Examinations<br>7 Spastic colon<br>12 Normal                            | G. Duodenal Drainage<br>17 Examinations<br>2 Cholesterol crystals<br>1 Ca Bilirubinate crystals<br>14 Normal          |
| C. Gastroscopy<br>7 Examinations<br>1 Superficial gastritis<br>1 Atrophic gastritis<br>5 Normal | H. Glucose Tolerance<br>27 Examinations<br>12 Reduced tolerance<br>15 Normal  |
| D. Serum Bilirubin<br>22 Examinations<br>1 Above 1.5 mg./100 cc.<br>21 Normal                   | I. Hippuric Acid (Intravenous)<br>22 Examinations<br>2 Below 0.5 gm.<br>4 0.5 to 1.0 gm.<br>16 Normal (above 1.0 gm.) |
| E. Blood Cholesterol<br>23 Examinations<br>5 Elevated (above 275 mg./100 cc.)<br>18 Normal      |   |

ance. It will be shown that this occurred in other groups as well as those having irritable colons. The test used was the Extton-Rose two dose method; all patients who had reduced sugar tolerance had two tests and no glycosuria. We cannot offer an entirely satisfactory explanation for this phenomenon unless it be that this test has revealed many sub-clinical instances of reduced hepatic function. The intravenous modification of the hippuric acid test was also suggestive of reduced hepatic function in six cases. It would be unwise to draw definite conclusions from these results, but they may be regarded as suggestive and justify further study.

It has been concluded from these findings that there is a high incidence of functional colonic disturbances in gall bladder disease, and that the dyspepsia between attacks of gall bladder colic is often due to this disturbance and not to cholecystitis or gall stones per se. It is also concluded that dyspepsia after cholecystectomy is likewise due to the colonic dysfunction in a majority of the cases.

\*Metamucil—furnished by G. D. Searle and Co.

Table II, Part 2, shows the next largest group of patients presenting persistent dyspepsia after cholecystectomy. It is not certain that these cases belong in a single group. There are similarities, however, which seem to justify the formation of a separate group which we have called unclassified dyspepsia and food intolerance. The same dyspeptic symptoms and intolerance to the usual food; namely, fats, cabbage, onions, beans, pork, and fried foods were present in all cases. There was no disturbance of bowel function in any case. No X-ray evidence of organic gastro-intestinal pathology was obtained. A striking feature was the patients' prompt improvement on large doses of bile salts.\* This improvement usually included increased tolerance to fats. This therapeutic response leads one to suspect that there may be a definite hepatic factor in this group since it seemed that increased bile flow and increased production of bile salts were beneficial (6, 7). These cases may be regarded as fat indigestion based on a relative deficiency of bile salts in the intestine (5). The laboratory and X-ray findings in this group are shown in Table IV.

TABLE IV

*Laboratory and X-ray studies on group I patients with unclassified dyspepsia*

|   |  |
|---|--|
| A. X-ray of Stomach and Duodenum<br>8 Examinations<br>8 Normal                                      | F. Gastric Analysis<br>7 Examinations<br>1 Achlorhydria<br>1 Hypochlorhydria<br>3 Hyperchlorhydria<br>2 Normal |
| B. X-ray of Colon<br>6 Examinations<br>6 Normal   | G. Duodenal Drainage<br>7 Examinations<br>3 Cholesterol crystals<br>1 Ca Bilirubinate crystals<br>3 Normal     |
| C. Gastroscopy<br>4 Examinations<br>4 Normal  | H. Glucose Tolerance<br>7 Examinations<br>3 Reduced tolerance<br>4 Normal                                      |
| D. Serum Bilirubin<br>7 Examinations<br>1 Above 1.5 mg./100 cc.<br>6 Normal                         | I. Blood Cholesterol<br>7 Examinations<br>7 Normal   |
| E. Hippuric Acid (Intravenous)<br>8 Examinations<br>1 Below 0.5 gm.<br>4 0.5 to 1.0 gm.<br>3 Normal |  |

Although the number of tests is small, there are some indications of a disturbance of hepatic function in the hippuric acid tests, the glucose tolerance tests, and the duodenal drainages. However, similar changes were seen in the control groups, and the tests are therefore of doubtful significance as far as relationship to clinical symptoms is concerned.

The remaining patients in Group I were instances of well-defined entities including diverticulitis of the colon, superficial gastritis, chronic pancreatitis, biliary dyskinesia, and a case of chronic pelvic inflammatory disease, the only case with primary pathology outside the gastro-intestinal tract. The laboratory and X-ray findings in these patients were not remarkable and conformed to those usually found in such cases. These results are shown in Table II.

Three groups of patients were studied simultaneously with those complaining of dyspepsia after removal of their gall bladders. These control patients were examined in exactly the same way as were those in Group I. The first group consisted of a number of patients selected from the clinic who had been diag-

nosed as having typical neurogenic irritable colon syndrome. These cases were selected for comparison because their dyspeptic symptoms so closely simulated those presented by the patients with gall bladder disease as well as by those who had persistent dyspepsia after cholecystectomy.

This group of patients is compared to the post-cholecystectomy group not to demonstrate a mere resemblance to the dyspepsia of gall bladder disease and the post-cholecystectomy syndrome, but to show that the dyspepsia and food intolerance are identical in the two conditions.

The next control group consisted of fifteen patients who had experienced complete relief of colic by cholecystectomy. These patients did not have dyspepsia. Examination of their X-ray and laboratory studies showed only two abnormalities which occurred rather frequently. The more common was decreased glucose tolerance. A suitable explanation is lacking. A few patients had moderately-diminished excretion of hippuric acid, but this was not sufficiently marked to suggest definite hepatic dysfunction. The third control group consisted of eleven patients who had suffered from colic and dyspepsia and were relieved of both by removal of their gall bladders. The laboratory and X-ray studies in this group revealed no evidence of associated gastro-intestinal pathology. We were again surprised to encounter a high incidence of decreased glucose tolerance in this group.

The most significant fact demonstrated by these patients was the usual close association between the colic and dyspepsia. In other words, they suffered from dyspepsia during and immediately after the attacks, but were relatively free of these symptoms in the intervals.

## SUMMARY

In analyzing the results of this investigation, one is impressed by the fact that no definite entity of gall bladder dyspepsia can be established. There was nothing in the histories to separate this dyspepsia from that originating from other sources. One finding seems important; if the dyspepsia is associated with the acute attack alone, then relief is likely to follow cholecystectomy. There was no difference in the food intolerance in the post-cholecystectomy group and that found in the irritable colon group. This was rather surprising in view of the commonly-held belief that fat intolerance is pathognomonic of gall bladder disease. The foods mentioned most often as causing dyspepsia were identical with those found in the so-called irritable colon syndrome. We are unable to explain adequately the frequent occurrence of abnormal glucose tolerance. There was no correlation between the degree of pathology found in the excised gall bladders and the clinical symptoms or relief by cholecystectomy. The various laboratory procedures revealed no uniform abnormalities.

While we do not suggest that the diseased gall bladder with stones should not be removed, we do feel that the patient should be informed of his chances for obtaining relief from dyspepsia. Every effort should be made to determine the true cause of the dyspepsia and, if possible, measures instituted to correct it before operation.

## CONCLUSIONS

1. No distinct entity of gall bladder dyspepsia could be established in a study of patients having a

\*Biliron—Ell Lilly and Co.

return of dyspeptic symptoms after cholecystectomy.

2. If the dyspepsia is intimately associated with the acute attack and there is no interval dyspepsia, relief is likely to follow cholecystectomy.

3. Various causes have been found responsible for the dyspepsia in a group of post-cholecystectomy patients.

4. Food intolerance in gall bladder disease is identical with that encountered in a variety of gastrointestinal disorders.

5. The colic of gall bladder disease is relieved, in most cases, by cholecystectomy; dyspepsia is not and should not in itself be an indication for cholecystectomy.

We are indebted to Drs. Mason Light and Joseph C. Reed for their assistance in this investigation.

### REFERENCES

1. Walters, W. and Snell, A. M.: Diseases of the Gall Bladder and Bile Ducts. W. B. Saunders and Co., Philadelphia, 1940.
2. Biscard, J. D. and Dornberger, R. G.: Study of 836 Cases of Gall Bladder Disease—Results of Medical and Surgical Treatment. *Nebraska Med. J.*, 23:374, 1938.
3. Street, A.: Diseases of the Gall Bladder and Bile Ducts, Symptomatology and Results of Surgical Treatment. *Southern Surg.*, 7:290, 1938.
4. Moore, E. C.: Chronic Cholecystitis with Reference to the Irritable Colon. *Western J. of Surgery, Obstetrics, and Gynecology*, 45:244, 1938.
5. Palmer, Walter L.: Gall Bladder Disease: Remarks on Symptoms, Diagnosis and Treatment. *International Clinics*, 1:111, 1935.
6. Rosenak, B. D. and Kohlstaedt, K. G.: Bile Salt Therapy in Liver and Gall Bladder Disease. *Am. J. Dis. Dis. Nutrit.*, 3:577, 1936.
7. Ivy, A. C. and Berman, A. L.: The Rationale of Bile Salt Therapy in Biliary Tract Disease. *Minn. Med.*, 22:815, 1939.

### DISCUSSION

DR. SARA M. JORDAN (Boston, Mass.): Mr. President and Members: Dr. Moser's paper, I think, is im-

portant because it calls attention again to the fact that we, as gastro-enterologists, should and do try to avoid unnecessary and unsuccessful cholecystectomies. It is a very legitimate aim of the gastro-enterologist. When we recall the days in which we struggled to determine accurately whether the Graham-Cole test was a help or not, we smile, because we know that it is, of course, one of our best aids in this aim.

It seems to me that one point about the Graham-Cole test perhaps should deserve a little emphasis, and that is the fact that functional conditions in the gall bladder, that is, poor emptying time, and so forth, were formerly stressed a great deal. In our opinion, at least, the functional condition of the gall bladder is often a temporary affair; that is, a failure of the gall bladder to contract after a fat meal, may occur today, but a month from now, after suitable treatment, this is not the case. Furthermore, secretory disturbances such as achlorhydria and other functional conditions in the gastro-intestinal tract, which may be temporary, must also be considered in the post-operative management of gall bladder disease and in the differential diagnosis between actual gall bladder disease and functional conditions.

The unsuccessful cholecystectomy, as Dr. Moser pointed out, can well be avoided if we consider these factors:

First, accurate diagnosis. In our opinion only the gall bladder with stones or that which we suspect to be carcinomatous, should be removed, and the other, the functional gall bladder, or the condition which simulates organic disease but actually is a functional disturbance, should be treated medically, at least for a time until an accurate check-up and observation can be made. Thank you!

## The Problem of Common Duct Stones: Further Experience with an Instrument for Visualizing the Interior of the Common Duct at Operation\*

By

MONROE A. McIVER, M.D.  
COOPERSTOWN, NEW YORK

AMONG the pathological conditions of the biliary system which are amenable to surgical treatment, stone in the common duct occupies an important place from the point of view of frequency and of seriousness of the secondary lesions which result.

It is, of course, impossible in many cases to be certain without opening the common duct whether or not a stone is present. But even after the duct has been opened, the difficulty of locating the stone, the possibility in the case of multiple stones that some may be overlooked and allowed to remain in the duct, and the uncertainty in some instances as to whether the obstruction is caused by a stone or a tumor—these problems remain, and have led to the development of an instrument for visualizing the interior of the common duct at operation (1), which I shall discuss after a resumé of some of the factors which enter into the situation.

Recent statistical data stress the frequency of common duct stones. Allen (2) reports the finding of stones in the common duct in 13% of biliary tract

operations; Lahey (3) reports that stones were removed from the common duct in approximately 20% of his patients operated on for gall stones; and Cheever (4) states that in 16.4% of his operations on the biliary tract common duct stones were encountered.

Certainly there is a tendency in the recent surgical literature to stress the importance of the problem and to broaden the old indications for exploring the common duct. The decision to carry out this procedure may be a simple one. If in operating upon a diseased gall bladder a stone can be palpated in the common duct, or if its presence can be indicated by injection of radiopaque medium into the duct, the diagnosis is, of course, obvious. If the duct is dilated, even though no stone can be palpated, most surgeons would agree that a search for a stone by direct methods should be made. In the absence of such evidence, the decision as to whether or not the duct is to be explored is a more difficult one.

The likelihood of finding a stone in the common duct is, of course, based on the patient's clinical history as well as on local findings. If a history of

\*From the Surgical Research Laboratory of the Mary Imogene Bassett Hospital.

Read at the Annual Meeting of the American Gastro-Enterological Association at Atlantic City, N. J., May 6, 1941.

jaundice, either with the present illness or in the past, can be obtained, one is naturally more suspicious of the presence of a stone in the common duct—although it might be pointed out in passing that in a recent series of cases of common duct stones, one or another of the classical triad of symptoms (jaundice, chills and fever, and colic) was frequently absent: approximately one-third of the patients had never been jaundiced, one-third did not have typical colic, and two-thirds had no chills and fever (5).

In addition to the above evidence of stones in the common duct, we find in the literature a long list of indications for exploring the duct. The authors consider it advisable to open the common duct if the cystic duct is dilated—if the gall bladder is fibrosed and contracted—if gross inspection of the gall bladder after removal reveals long-standing infection, as indicated by changes in its mucosa and wall—if upon needling the common duct the bile obtained is cloudy, black or contains flocculi—if sand and small stones are found in the gall bladder—or if there is a thickening of the head of the pancreas (2, 3).

Granted that a decision to open the duct has been based on adequate premises, there is still the problem of locating the stones. Among the methods in current use are the various well-known maneuvers of probing the duct and palpation, either separately or in combination. At times, if the duct is sufficiently dilated, direct exploration with the finger is helpful; and translumination of the surrounding tissues by passing a Cameron light into the duct has been used (6). If these methods appear to be inadequate, the duct may be injected with a radiopaque medium at the time of operation and X-ray films taken immediately (7-8).

Even with these methods, stones may be overlooked. It is difficult to estimate the frequency of "missed" stones. Mayo (9) in 1923 reported that in one-third of their cases that came to autopsy following exploration of the common duct it was found that all the stones had not been removed; and Young (10), in 1929, in an analysis of autopsy material from the Massachusetts General Hospital, also reported many "missed" stones in the common duct. Although recent figures may be better, most surgeons have at times misgivings that all stones may not have been removed even after they have made a thorough search. There are also indirect indications in the literature that the problem of missed stones still exists. Several recent writers (11-12) for example, stress the importance of dilating the sphincter of Oddi so that small stones which may have been overlooked in the common or hepatic duct may be passed. It is also a well-accepted practice to take cholangiograms during convalescence before the drainage tube is removed from the common duct in order to make sure that no stones have been overlooked—although it is an obviously embarrassing situation if they are found at that late date. And, lastly, a number of articles have recently appeared outlining the non-operative management of stones that may have been left in the common duct (13-14).

With a view to a more direct approach to detection of common duct stones and the study of other lesions of the extra-hepatic ducts, an instrument (the choledochoscope) for direct inspection of the interior of the common duct at the time of operation is being used. Fig. 1 shows a photograph of the instrument. The shorter right-angled portion, which is inserted directly into the common duct, is about 7 cm. in length

and 5 mm. in diameter, and bears a light at its tip. The opening for observation and irrigation is just behind the light.<sup>3</sup> The long upright portion is about 45 cm. in length and 1 cm. in diameter. This allows observation at a distance sufficient to avoid soiling the operative field. Connections for battery and water are placed about 9 cm. from the eyepiece, in order to avoid contaminating the hands during the use of the instrument.

The instrument is used as follows. The common duct is opened between traction sutures in the usual manner and the end of the instrument bearing the light is passed into the duct. At the same time, the finger is placed at the heel of the instrument to guide it and also to protect the liver from injury. It is desirable to maintain a constant flow of water through the irrigating system during the period of observation, in order to wash out any bile which may be

<sup>3</sup>Since writing the above, the author has been experimenting with a somewhat shorter right-angled portion, but sufficient data has not been accumulated to pass on its merits.

<sup>4</sup>The lens system was devised by Mr. Frederick C. Wappler of the American Cystoscope Company.

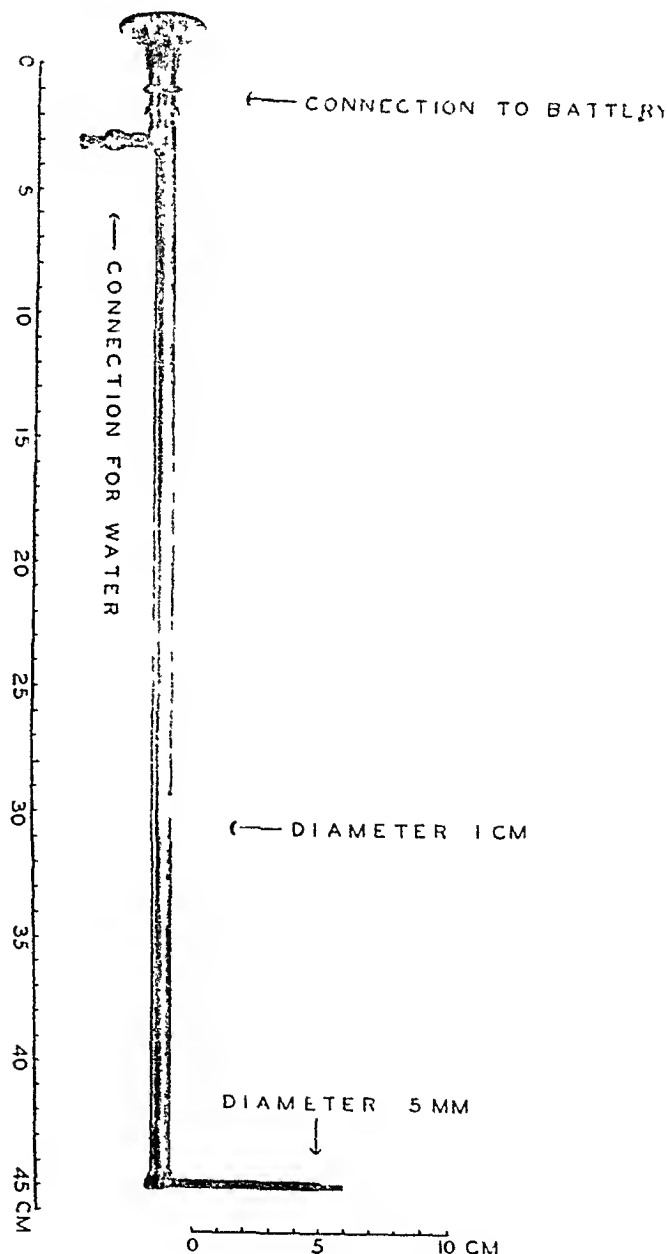


Fig. 1. The choledochoscope (McIver (1)).

present and also to push the walls of the common duct away from the lens sufficiently to permit a clear view. As soon as the bile is completely flushed out, observation is started. It is desirable at this point to turn off the main operating room light—further darkening of the room is not essential. A good view of the walls of the duct is usually obtained. If the lower portion of the duct shows no pathological lesion or foreign body, the instrument is withdrawn and reinserted toward the liver, so that the upper portion in the region of the hepatic ducts may be inspected.

Fig. 2 shows a common duct stone that was visu-

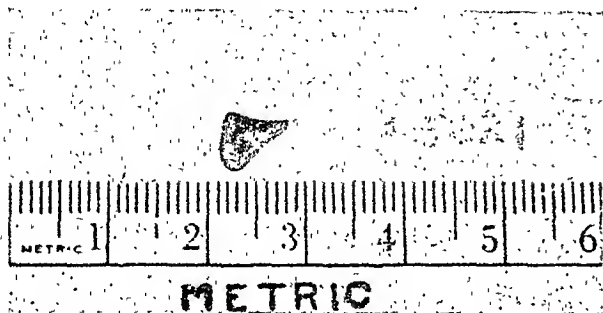


Fig. 2. Stone visualized in the lower portion of the common duct and removed.

alized with the choledochoscope at operation and subsequently removed. The salient features of this case are as follows:

Case 1. H. K., History No. 21194, a male, 71 years old, was admitted to the hospital because of attacks of chills and fever which had occurred 5 times during the past month. There had been no definite colic, but a history of vague gastro-intestinal symptoms for 2 years. The patient was not jaundiced on admission, nor was there a history of jaundice.

A few days after entrance to the hospital the patient had another chill. Cholecystograms, following oral administration of the dye, did not visualize the gall bladder. In spite of the absence of jaundice and the questionable cholecystograms, it was felt that this patient probably had a common duct stone, and he was operated upon.

At operation the gall bladder was found to be thin-walled and somewhat distended, with no adhesions to surrounding viscera. After emptying the gall bladder of bile, thorough exploration of this organ was made but no stones were found. The common duct appeared dilated, but no stones could be palpated. There was, however, definite hardness of the head of the pancreas, which interfered with adequate palpation of the lower portion of the duct. The duct was opened and inspected with the choledochoscope. The stone shown in Fig. 2 was visualized in the lower end of the duct and was removed, together with a second stone lying behind the first, and some amorphous, sandy material. After the duct had been carefully washed out, it was again inspected and no further stones were seen. The hardness of the head of the pancreas probably represented an associated pancreatitis. Convalescence was uneventful.

Fig. 3 shows 3 small calcium bilirubinate stones which were similarly visualized with the choledochoscope and removed. Fig. 4 shows the gall bladder, removed from the same patient, with similar stones lying in it. The clinical history of this patient was interesting:

Case 2. M. M., History No. 18266, a 46 year-old woman, mother of 9 children, was admitted to the hospital because

of attacks of severe epigastric pain. The patient had never been jaundiced and had had no chills or elevation of temperature. In association with these attacks she had been hospitalized 3 times. On 2 of these admissions the blood amylase was noted to be markedly elevated. Cholecystograms had been taken on 3 occasions; the gall bladder was visualized well in all of the examinations and nothing abnormal was noted in the first 2. In the last, small areas of increased density, somewhat suggestive of gall stones, were described. Gastro-intestinal series was negative; icteric index never above normal. On the previous admissions it had been thought that the patient had acute pancreatitis which might possibly be associated with biliary or pancreatic calculi, although none could be demonstrated. The attacks were becoming so severe that it was decided that an exploratory operation should be carried out.

Operation disclosed a gall bladder the walls of which seemed somewhat thickened and moderately distended. Palpation revealed no stones in the gall bladder. There appeared to be some thickening of the head of the pancreas, but no calculi could be palpated in the pancreatic ducts or the common duct. The cystic and common ducts appeared slightly dilated. The common duct was opened between traction sutures and explored with the choledochoscope. In the lower portion of the duct a small, black, foreign body was visualized. The instrument was withdrawn, and by a scoop and irrigation the 3 small calculi shown in Fig. 3 were removed. When the gall bladder was opened, subsequent to removal, a large number of small calculi of similar physical characteristics were found, as shown in Fig. 4. These stones proved to be composed of calcium bilirubinate—a type of stone that usually is formed in the common duct rather than in the gall bladder (15-16). In this instance, however, in view of the large number of smaller stones of a similar character in the gall bladder, it would seem reasonable that the stones had formed in that organ and been passed into the common duct. Also it seems probable that the patient's previous attacks of colic and acute pancreatitis had resulted from the blockage of the pancreatic duct by one of these small stones. The patient had an uneventful convalescence and to date has had no further attacks of colic.

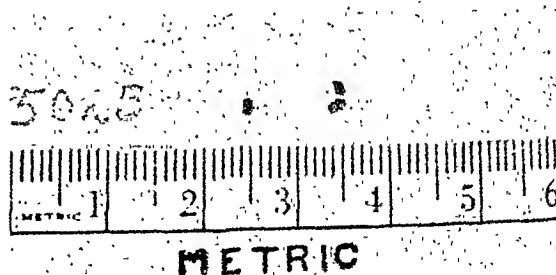


Fig. 3. Calcium bilirubinate stones removed after visualization, Case 2.

It is interesting to note that this patient also had no jaundice and that the icteric index was only 3.

Foreign bodies other than gall stones in the common duct, while a rarity, occur more frequently than one might realize (17-18). It is rather curious that in the small series of cases that have been investigated with the choledochoscope, such a foreign body should have been encountered. This patient (F. M., History No. 19330) was a woman of 58, jaundiced, and with calculi in the gall bladder. In the course of exploring the common duct, a piece of coarse hair was seen, lying near the ampulla. This was removed, and proved to be



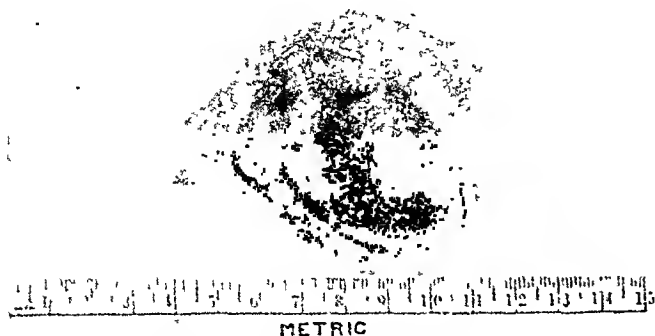


Fig. 4. Gall bladder, Case 2, showing numerous stones similar to those found in the common duct (See Fig. 3).

a horse hair. This probably played no part in the clinical history, but was of some interest as a curiosity.

In regard to obstructions of the common duct by neoplasms, only a few cases in which such a lesion was present have been explored with the choledochoscope. The value of the instrument here is chiefly on the negative side—that is, in cases where there is some difficulty in telling whether the obstruction is due to a neoplasm or to a stone with surrounding inflammatory reaction. This differential diagnosis may be a real problem, as illustrated by 2 cases in Young's (10) series, in which a "missed" stone found at autopsy had been overlooked due to the fact that the stone with the surrounding inflammation had been erroneously diagnosed as carcinoma of the head of the pancreas at the time of operation. That the choledochoscope may

be of use in such a situation is illustrated by the following case. The patient (E. W., History No. 7934) was an elderly woman, deeply jaundiced. At operation a hard, nodular mass, a few centimeters in size, was felt in the head of the pancreas. This was thought to be a carcinoma, but there was some question whether it might instead be an inflammatory reaction around a stone impacted at the ampulla of Vater. In view of the uncertainty as to the etiology of the obstruction by palpation alone, the lower end of the common duct was inspected with the choledochoscope. The lower end of the duct was found to be completely obstructed, but no evidence of stone could be seen. The diagnosis of carcinoma of the head of the pancreas was made and subsequently confirmed.

In another instance a patient (H. M., History No. 10477) with jaundice and cholelithiasis was explored. A small mass was found at the hilus of the liver, extending into the liver substance. Inspection through the instrument showed complete stenosis of the left hepatic duct slightly above the bifurcation, while a clear view could be had of the right duct. It was felt that this obstruction of the duct was due to a carcinoma, although a positive diagnosis could not be made because the inadequate scrapings from the duct mucosa showed no carcinoma cells. However, the diagnosis was confirmed at autopsy several months later.

In conclusion, it is believed that enough work has been done with the instrument to warrant its consideration by those who are not completely satisfied with their present methods of detecting common duct stones. It is hoped that it may be of some help to them in their work and possibly in obtaining a clearer understanding of the various pathological lesions of the extra-hepatic ducts.

#### REFERENCES

- McIver, M. A.: An Instrument for Visualizing the Interior of the Common Duct at Operation. Preliminary Note. *Surgery*, 9:112, 1941.
- Allen, A. W.: The Diagnosis and Treatment of Stones in the Common Bile Duct. *S. G. O.*, 62:347, 1936.
- Lahey, F. H.: Common and Hepatic Duct Stones. *Am. J. Surg.*, 40:209, 1938.
- Cheever, D.: Methods and Results in Surgical Treatment of Diseases of the Biliary Passages. *New England J. Med.*, 213:463, 1935.
- Trueman, K. R.: Symptoms of Common Duct Stone. Review of 219 Cases. *Proc. Staff Meetings Mayo Clinic*, 15:283, 1940.
- Glenn, F.: Surgery of the Gall Bladder and Biliary Tract. *Ann. Surg.*, 103:77, 1936.
- Robins, S. A. and Hermanson, L.: Cholangiography—A Modified Technique for the X-ray Visualization of the Bile Ducts During Operation. *S. G. O.*, 62:684, 1936.
- Hicken, N. F., Best, R. R. and Hunt, H. B.: Cholangiography. Visualization of the Gall Bladder and Bile Ducts During and After Operation. *Ann. Surg.*, 103:210, 1936.
- Mayo, W. J.: Surgery of the Hepatic and Common Bile Ducts. *Lancet*, 204:1299, 1923.
- Young, E. L.: Possibilities of Failure in the Removal of Stones in the Biliary Tract. *New England J. Med.*, 200:1145, 1929.
- Allen, A. W. and Wallace, R. H.: The Surgical Management of Stone in the Common Bile Duct. *Ann. Surg.*, 111:838, 1940.
- Walters, W.: Lesions of the Extrahepatic Biliary Tract. *J. A. M. A.*, 111:2477, 1938.
- Best, R. R. and Hicken, N. F.: Non-operative Management of Remaining Common Duct Stones. *J. A. M. A.*, 110:1257, 1938.
- Burgess, C. M.: Solution of Gall Stones. *J. A. M. A.*, 114:2372, 1940.
- Mentzer, S. H.: The Pathogenesis of Biliary Calculi. *Arch. Surg.*, 14:14, 1927.
- Carter, R. F., Greene, C. H., Twiss, J. R. and Hotz, R.: Etiology of Stone in the Common Bile Duct. *Arch. Surg.*, 40:103, 1940.
- Toland, C. G.: Foreign Bodies in the Biliary Tract. *Ann. Surg.*, 98:904, 1933.
- Baumgartner, C. J. and Lasky, I. I.: Cherry Stem in Common Duct Stone. *J. A. M. A.*, 115:2168, 1940.

## Lipophagic Granulomatosis of the Enteric Tract\*

By

SEATON SAILER, M.D.

and

R. J. MCGANN, M.D.

CINCINNATI, OHIO

**G**RANULOMATOUS lesions characterized by the presence of great numbers of large mononuclear cells having an abundant cytoplasm richly interspersed with coarse fat particles, droplets of fat lying free or

partially phagocytized by multinucleated foreign body giant-cells, and varying admixtures of small lymphocytes, plasma, polymorphonuclear, and fibroblastic cells, have been classified histologically as lipogranulomas. These reactions are predominantly local in character and confined to adipose tissue. Most frequently they have been described in the breast (1), subcutaneous

\*From the Department of Pathology, University of Cincinnati, College of Medicine, Cincinnati, Ohio.

Read at the Annual Meeting of the American Gastro-Enterological Association at Atlantic City, N. J., May 6, 1941.



tissues of the trunk and extremities (2, 3), retroperitoneal and mesenteric fat depots (4). Various mechanical, thermal, chemical, hormonal, or obscure toxic agents may be instrumental in producing these lesions (5, 6) but the essence of the pathological process appears to be a local necrosis of fat tissue with liberation of lipolytic ferments from the damaged cells. Thus freed and sometimes partially saponified fats accumulate which tend to behave as foreign bodies to their immediate environment and call forth a special type of granulomatous phagocytic cellular response. The terms traumatic fat necrosis, fat granuloma, oleogranuloma, subcutaneous fat autolysis, cystic steatonecrosis, and lipophagic granuloma (7) have been employed interchangeably in describing this condition. The last mentioned term appears preferable as it emphasizes the fat resorption phenomenon and avoids confusion with that group of diseases classified as lipoid granulomas.

In addition to these predominantly local lesions dependent on changes within fixed fat tissues, a far less frequently occurring, but histologically identical reaction has been described occupying the inner coats of the small intestine and distorting the architecture of the draining mesenteric and adjacent lymph nodes. Clinical and pathological data on cases apparently belonging to this group are briefly summarized from the literature in the following paragraphs.

The first case was published by Whipple (8) in 1907 as "A hitherto undescribed disease characterized anatomically by deposits of fat and fatty acid crystals in the intestinal and mesenteric lymphatic tissue." The patient, a 36 year-old, male physician, had enjoyed good health until 5 years before hospitalization when he began to suffer from polyarthritides. These attacks were unassociated with fever but recurred frequently and were accompanied by gradual loss of weight and strength. A few months before admission a moderate diarrhea began with the passage of cream colored fluid or semi-fluid stools containing a great excess of neutral fats and fatty acids and little bile. A mass became palpable in the lower abdomen. There was no history of jaundice or anorexia. A moderate secondary anemia was present: total white blood counts were within normal limits with a relative increase in the number of small and large lymphocytes and a marked increase in the polymorphonuclear eosinophiles. There was slight general pigmentation of the skin. Sputa examination were negative and the urine showed no significant changes. The tuberculin test was negative. The patient's abdomen was explored surgically and he died shortly thereafter. At autopsy, the mesenteric lymph nodes were enlarged and firm, some measuring 3 to 4 cms. in diameter. Their cut surfaces were translucent, opaque, pale-yellow studded with fine yellow grains; occasional cyst-like pockets containing fatty material were noted. The thoracic duct was dissected out and appeared unobstructed. Its fluid contained numerous small highly refractile droplets and rosettes of pale-greenish acicular crystals, as well as many mononuclear leucocytes and mast cells. A stained smear showed no bacteria. Chemically the mesenteric

nodes consisted chiefly of neutral fats. Saponification number of one of the fractions was 144.4. Microscopic sections taken from various levels of the jejunum and ileum showed extensive lipogranulomatous changes in the mucosa and submucosa with large quantities of fat and fatty acid crystals distributed both intra- and extra-cellularly. Small, recent and old hemorrhages were present in the mucosal villi. The muscle coats were normal. The serosa showed an organizing non-specific inflammatory reaction. The mesenteric nodes exhibited extensive lipophagic activity with numerous multinucleated giant-cells engulfing fat droplets and many dilated endothelial lined spaces containing fat and clusters of foam cells. Tissue treated by the Levaditi method exhibited great numbers of peculiar rod-shaped structures whose identification was uncertain. Because of the extensive scarring within some of the mesenteric nodes, the reaction was believed to be older in this location than in the intestinal mucosa, though in general the reaction was the same. In addition to the changes in the intestinal tract, the heart was considerably enlarged, presenting an obliterative pericarditis and a vegetative endocarditis of the aortic valve. The lungs showed an organized pleuritis and subserous hemorrhages. The pancreas appeared normal. The liver, kidneys, spleen and remaining organs deserved no comment.

Blumgart (9) sometime later reported on 3 fatal cases of malabsorption of fat occurring in early middle life. All had complained of general asthenia, diarrhea, progressive weight loss and exhibited moderately severe anemia. None gave a history of polyarthritides, fever, jaundice, or purpura. The anemia was of the secondary type but with a color index of approximately 1. The white blood counts were within the normal range. In 2 of the cases tetany was present. There was no excess skin pigmentation. The pancreatic lipolytic enzyme titer was considerably reduced in one case and no free hydrochloric acid was present in the stomach of 2 cases in which it was tested. Post-mortem studies on one case showed a non-specific hyperplasia of the lymphatics of the small intestine and mesenteric nodes. A second case showed a chylous ascites without demonstrable obstruction of the thoracic duct, which was carefully dissected. The small intestine submucosa contained numerous large mononuclear cells and multinucleated giant-cells with a finely vacuolated cytoplasm and apparently filled with fat. The mesenteric nodes were enlarged, soft, and cheesy in consistency but no details were given, as to their histology. The pancreas was normal. The third case showed numerous collections of fat-laden phagocytes in the submucosa of the small intestine with many dilated vessels. Many small circular mucosal ulcers were present in the lower jejunum. The mesenteric lymph nodes were described as definitely enlarged with microscopic evidence of chronic lymphadenitis and hyperplasia. Pathologic pancreatic changes were absent, although lipolytic ferment was reported reduced during life. There were no other noteworthy changes in the internal viscera.

Fleischman (4) next contributed a case of a 38 year-old man with a long history of arthritis and

progressive weight loss. A painful feeling of compression and tightening in the abdomen began the year prior to hospitalization. At laparotomy, a mass of firm nodes, double the size of a man's fist, were found at the root of the small intestine. Biopsy studies revealed granulation tissue formation with many large multinucleated foam cells and large fat cells. Post-operative X-ray therapy was applied over the abdomen but the patient failed to improve clinically. At autopsy, 2 months later, the large mesenteric mass was greatly reduced in size, being composed of multiple, sharply circumscribed, nodules reaching plum-size. Microscopic examination of these nodules revealed the histologic picture of a lipophagic granuloma with multinucleated foreign body giant-cells and calcium soap crystals. The pancreas exhibited some old interstitial scarring. The small intestine showed only atrophy of the mucosa with slight cellular infiltration of the submucosa. Old obliterative pericardial adhesions were also noted and there were small hemorrhages in the pleura.

Jarcho (10) published an account of steatorrhea with unusual intestinal lesions in a 37 year-old male who during the previous 15 years had suffered from repeated attacks of arthritis. A watery diarrhea had been present for at least 2 years and presumably contained considerable fat although results of quantitative chemical examination were not given. An attack of painless jaundice lasting 1 week had been present 2 years before hospitalization. A general pigmentation of the skin was noted on admission. The stools were constantly guaiac positive and a slight secondary anemia became progressively severe. At autopsy, lipogranulomatous lesions with phagocytosis of free fat droplets by large mononuclear and foreign body giant-cells were present in the mucosa and submucosa of the jejunum and ileum and in the mesenteric lymph nodes. Throughout these tissues the lymph channels appeared dilated and filled with fat. In addition, the heart showed rheumatic vegetations of the mitral and tricuspid valves and Aschoff bodies in the myocardium. Pericardial and pleural adhesions were present.

In discussing the diarrhea of pancreatic insufficiency, Boeck (11) described a case of a 45 year-old, male physician suffering from a persistent steatorrhea and progressive loss of weight. Gastric achlorhydria and a moderate secondary anemia were present. A laparotomy was performed and a biopsy taken from a large mass of lymph nodes at the mesenteric root of the small intestine. The histological picture described appears to be that of a lipophagic granuloma. Following X-ray therapy the diarrhea ceased almost entirely, also the steatorrhea. During the next 4 months, the patient gained 7 pounds but succumbed during the 5th post-operative month from acute cardiac decompensation. At autopsy, the mesenteric glands appeared normal and no evidence of fat and cholesterol deposits were present. Some fatty deposits occurred in the walls of the small intestine with mucosal atrophy. The pancreas, liver, and adrenals appeared normal.

Korsch's case (12) was that of a 60 year-old male who had intermittent joint pains for 10 years. During the previous year he complained of appetite loss, fre-

quent feeling of pressure and fullness in the upper abdomen with considerable loss of weight. A palpable mass in the upper left abdomen was painful on pressure. There was a moderate secondary anemia. At autopsy, a fist-sized collection of enlarged lymph nodes was present at the mesenteric root. Scattered small, blackish-grey flecks were seen stippling the mucosa of the entire small bowel. Histological examination of these revealed lipogranulomatous aggregates in the mucosa and submucosa of the small intestine and the lymph node reaction was typical of this condition. The thoracic duct was not examined but the nodes of the mediastinum and along the trachea showed changes similar to the mesenteric and retroperitoneal nodes, possibly, the author believed, the reaction to a back-flow of abnormal fat from the duct. No doubly refractive fat was found with polarized light. Chronic verrucous endocarditis of the aortic, and a scarred, calcified mitral valve, with old obliterative pericardial adhesions were found in the heart. The pancreas was intact.

Hill (13) has recently reviewed cases reported in the literature as mesenteric chyladenectasia. Some of these appear to us comparable to the pathological picture of lipophagic granuloma. He added the case of a 60-year male who complained of vomiting, diarrhea, and epigastric pain of 2 months' duration. The patient suffered from a similar attack a year before. He was extremely emaciated and secondary anemia was present, but his appetite remained good throughout his illness. White blood counts were normal. At autopsy, all the mesenteric nodes were enlarged, ranging from 0.8 to 3.0 cms. in diameter. They were firm, smooth, discrete, and on section exhibited a cystic, spongy appearance. Fatty material exuded from the small cystic spaces. Microscopic examination of the enlarged lymph nodes described prominently dilated lymph spaces with a cellular reaction compatible with that of lipophagic granuloma. A definite filling with fat and some distention of the lacteals and associated lymphatics was present in the small intestine, but no mention was made of the cellular response of the stroma, if any. The pancreas showed a definite increase in the interstitial fibrous tissue, particularly about the duct system. The author considered the lymph node lesions due to dilatation by chyle, with subsequent breakdown and inspissation of the emulsion. An obliterative pericarditis was present.

Reinhart and Wilson (14) presented a case of malabsorption of fat in a 74 year-old male who complained of an enlarged abdomen and constipation for 1 year. The patient had been well heretofore, but began to note vague abdominal discomfort after meals forcing him to reduce his food intake. During the ensuing year he lost 35 to 40 pounds in weight. There was no history of rheumatism, jaundice, or diarrhea. A moderately severe, generalized pruritus was present. Red blood corpuscles 3,400,000; white blood corpuscles 10,700; 25 per cent polymorphonuclear neutrophils; 59 per cent lymphocytes, and 10 per cent monocytes. Subsequent counts revealed a moderate leucocytosis with a considerable relative increase in lymphocytes. Icterus Index 7. Wassermann and Kahn tests were 4 +. Five paracenteses were done for abdominal distention and straw-colored fluid was removed. He was

discharged after 30 days, but returned 5 days later with marked distention, shortness of breath and urinary frequency. Abdominal tap yielded 4 liters of cream colored fluid. Five days later another 8 liters of similar fluid were removed. He died suddenly on the 10th day. At autopsy, the abdominal cavity contained about 6000 ccs. of cream colored fluid of milky consistency. The liver was pale brown and presented the cut appearance of a finely lobular portal cirrhosis. Marked enlargement of the lymph nodes was present at the root of the mesentery and the entire peripancratic group was involved, ranging in size from 1 to 4 cms. Numerous small cysts were seen on cut section from which fatty granules and semi-solid material could be expressed. Many of these nodes were the site of recent hemorrhage. The thoracic duct was not dissected out. Microscopically the villi of the small intestine were broadened, their stroma filled with large number of cells which were predominantly small lymphocytes. The lymphatics were prominently dilated. The lymph nodes also contained numerous dilated spaces having the general aspect of lymph sinuses filled with large amorphous conglomerations, which gave characteristic staining reactions for fat with Scharlach R and Nile Blue sulphate. Surrounding these were numerous vacuolated mononuclear macrophages and multinucleated giant-cells. The fat tissue enveloping the lymph nodes, blood vessels, pancreas, and kidney contained many small lymphocytes, presenting a leukemic type of infiltration. Slight interstitial pancreatic fibrosis was noted with focal epithelial metaplasia of the small ducts and some dilatation of the lymphatics. Numerous tissues stained for *Treponema pallidum* were negative.

The following case has been under observation intermittently over a period of 2 years in the Arthritic Clinic of the Out-Patient Department preceding admission to the Medical Ward of the Cincinnati General Hospital.

#### CASE REPORT

J. M. A 45 year-old, white, male, carpenter, was admitted to the Medical Ward of the Cincinnati General Hospital on September 17, 1940, complaining of abdominal pain, weakness, loss of weight, anorexia, and marked epigastric discomfort after eating. The patient dated the onset of these symptoms in March, 1940, at which time he experienced an attack of generalized edema. He claimed this accumulated within a period of 24 hours and was unaccompanied by any prodromata. There was associated oliguria with passage of small amounts of dark red urine. The edema disappeared within 2 days following administration of an intravenous diuretic by his local physician. The patient remarked that he had never felt entirely well since this episode. Ankle edema recurred and has been present more or less constantly since March. There was some associated exertional dyspnea but no orthopnea or paroxysmal dyspnea. At times a vague fluttering sensation was noted over the precordium. These complaints were accompanied by gradually increasing generalized weakness. His appetite had been poor for the last 6 months and he lost about 20 pounds in weight. Marked epigastric discomfort after eating, which he described as a "bloating sensation," was present during this period but was not related to any particular type of food; relief was frequently obtained by taking soda. During the last week he suffered from abdominal distention and cramping pains radiating across the lower abdomen up to the umbilicus.

The pain was almost constant during the day but it did not interfere with sleep. There was no nausea or vomiting. For the past 4 or 5 days his stools have been black and soft. He has had a tendency to constipation for the past several months; one brief episode of diarrhea occurred 2 months ago. There was no history of abnormally formed, acholic, or grossly bloody stools. The patient stated that during the past 6 months he developed a slight but increasing yellowish tinge to his skin. He also had a cough for the past few months occasionally raising a little yellowish-green sputum. His past history revealed that approximately 5 years before admission he developed pain, swelling, heat, and redness about his right elbow which lasted for 2 weeks and subsided without medication. A year later his right ankle and foot became similarly involved. Within the 3 years, subsequent intermittent attacks have affected the hips, spine, shoulder and right hand. During the past year the pain has been limited to both ankles and considerably aggravated on walking. There is no history of gonorrhea or syphilis. He had bronchopneumonia in 1919, and a hemorrhoidectomy in 1936. No family history of tuberculosis or rheumatism.

Physical examination on admission revealed a fairly well developed, poorly nourished, 45 year-old, white, male, in no apparent distress, alert and cooperative. Temperature 98; pulse 80; respiration 22; blood pressure 94/50. The skin of the entire body presented a peculiar light yellowish bronze hue. A few freckles and pigmented moles were present over the shoulders. The nail beds and mucous membranes were pale. The sclerae were clear, the pupils regular, equal and reacted well to light and accommodation. The fundi were normal. All the teeth and both palatine tonsils had been removed. The tongue protruded in the midline without tremor; it was slightly pale but not unduly smooth. Small, shotty lymph nodes were present in the epitrochlear and inguinal regions. The chest was symmetrical and expanded equally. A few moist rales were heard just to the left of the right lung apex and over the 4th and 5th interspace in the right anterior axillary line. No enlargement of the heart was noted. Murmurs were absent, the rate was regular and the sounds rather distant. The stethoscope left a pitted imprint on the chest wall. The abdomen was moderately distended and tympanitic. No fluid wave was present. Slight tenderness to palpation was noted in the left lower quadrant. Liver, spleen and kidneys were not palpable. Peristalsis appeared active. A 2+ pitting edema was present over the lower legs and sacrum. Some hindrance of motion was present in both wrists and the ankle joints were ankylosed. No abnormalities were noticed on neurological examination. X-ray examination of the ankle joints revealed changes compatible with those of rheumatoid arthritis. A slight haziness seen at the left base of the chest films was believed due to chronic bronchitis but other significant changes were absent.

Gastro-enterological examination on September 24, 1940, showed the esophagus and stomach within normal limits. The duodenal cap was not deformed and visualized well. Some dilatation was present in the second portion of the duodenum due apparently to hypomotility. Further on in the jejunum hypomotility was conspicuous and definite puddling of the barium was noted with occasional irregular areas of spasm. The valvulae conniventes were irregular, distorted and somewhat indistinct; in a few areas they appeared thickened and unduly separated (Fig. 1). At 6 hours there was still a very small amount of barium within the stomach. The greater portion occupied the lower small bowel. The colon had lost its normal haustral markings. It contained scattered portions of barium and some were present in the rectum.

A flat plate of the abdomen taken on October 9, 1940, showed an increased haziness throughout with loss of

soft tissue detail suggesting the presence of fluid. The loops of small bowel were rather widely separated and showed irregularity of their contours, irritability and segmentation. Blood studies showed as follows:

change. The abdominal distention and discomfort continued. Peristaltic movements became indiscernible. An abdominal paracentesis was done on his 20th hospital day and 3500 ccs. of clear amber fluid, having the character

### Blood Studies

| Date    | Hemoglobin | Erythrocytes | Leucocytes | Polymorpho-nuclears | Lymphocytes | Remarks  |
|---------|------------|--------------|------------|---------------------|-------------|--|
|         | Gm.        |              |            | %                   | %           |  |
| 9-17-40 | 8.8        | 4,400,000    | 12,000     | 92                  | 8.0         |  |
| 9-20-40 | 7.0        | 3,600,000    | 12,500     |                     |             |  |
| 9-26-40 | 7.0        | 2,560,000    | 9,100      | 88                  | 10.0        | Reticulocytes 3.85%<br>Monocytes 2.0%<br>Platelets 619,000<br>H.C.T. 22<br>M.C.V. 90<br>M.C.H. 20<br>M.C.H.C. 22 |

The anemia was of the hypochromic type with regeneration such as is noted in chronic blood loss. Despite repeated transfusions, subsequent counts were:

### Blood Counts

| Date     | Hemoglobin | Erythrocyte Count | Leucocyte Count |
|----------|------------|-------------------|-----------------|
|          | Gm.        |                   |                 |
| 10-1-40  | 8.0        | 3,010,000         | 5,650           |
| 11-18-40 | 8.25       | 2,810,000         | 1,700           |

Daily stool examinations during the first month showed variation in color from dark brown to black with a consistent 3+ guaiac reaction. Most of the stools were semi-solid in consistency. After the first month they were reported as clay colored on two occasions and usually light tan to brown in color. Guaiac reactions were negative on 10 daily examinations, but more often showed a 1+ to 2+ positive. Gastric analysis showed complete absence of hydrochloric acid after histamine. Blood proteins were reported as follows:

| Date    | Total Protein | Albumin | Globulin | A/G Ratio |
|---------|---------------|---------|----------|-----------|
|         | Gm. %         |         |          |           |
| 9-25-40 | 6.0           | 3.4     | 2.6      | 1.3/1     |
| 10-2-40 | 3.0           | 1.9     | 1.1      | 1.7/1     |
| 11-4-40 | 2.2           | 1.2     | 1.0      | 1.2/1     |

Kahn and Wassermann Tests: Negative

Serum sodium varied from 229 mmm. % to 383 mmm. %.

Plasma chloride varied from 559 mmm. % to 606 mmm. %.

Glucose Tolerance: Fasting 77 mgm./100 ccs. of blood.

1 hour 91 mgm./100 ccs. of blood.

1 hour 86 mgm./100 ccs. of blood.

2 hours 73 mgm./100 ccs. of blood.

3 hours 70 mgm./100 ccs. of blood.

One blood culture: Negative.

Blood urea nitrogen: Ranged from 36 mgm. % to 41 mgm. %.

Repeated urine examinations showed no abnormalities.

Bleeding, Clotting, and Prothrombin Time: All within normal range.

The patient was placed on symptomatic treatment with a high protein diet and adequate amounts of riboflavin, Vitamin B<sub>1</sub> and B<sub>2</sub>. His course while in the hospital was progressively downhill. Because of the marked asthenia, anorexia, vomiting, persistent low blood pressure, which ranged between 74/50 to 110/70, and a suggestive bronzing of the skin, he was given a therapeutic trial with desoxycorticosterone acetate (pericortin) without appreciable

of a transudate, were removed. Culture and guinea pig inoculation of the fluid were negative. Following this, the patient felt subjectively improved for the ensuing 2 weeks. Vomiting subsided and there was a decided improvement in his appetite and ability to retain increasing amounts of food, although physically he appeared about the same. Hypotension remained unchanged and stool examination persisted guaiac positive. Abdominal fluid and distention gradually reappeared so that 3 weeks later another abdominal tap was performed. This time 2500 ccs. of watery fluid was removed. Again he obtained relief but the fluid began to reaccumulate faster than before. On the 50th hospital day, the patient suddenly developed severe pain around the umbilicus which was constant and boring in character. The abdomen became diffusely tender without rebound tenderness. Peristalsis was active. This was accompanied by profuse vomiting. These symptoms became more aggravated and the following day he succumbed.



Fig. 1. Sept. 24, 1940. 6-hour film showing irregularity and distortion of valvulae conniventes of small intestine with puddling of barium.

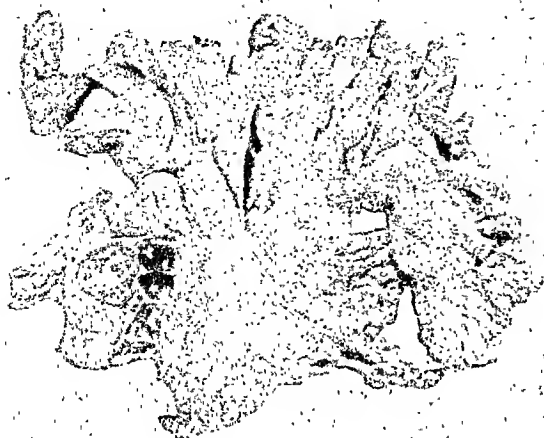
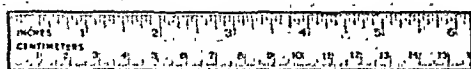


Fig. 2. Enlarged mesenteric lymph nodes. Cut section of large node shows a cyst which contained fatty and oily material.

Throughout his entire hospitalization he remained afebrile and pulse and respiration rates never were significantly elevated.

### NECROPSY

An abstract of the necropsy performed 4 hours post-mortem is as follows: The body, 164 cms. in length, is that of a well developed, poorly nourished white male appearing his stated age of 45 years. There is a 2+ edema of the ankles extending up both legs to just below the knees, also moderate edema of the scrotum. The abdomen is distended and rounded. The skin of the entire body is dry and presents a brownish discoloration about the face, neck, and over the dorsal aspect of both hands. The superficial inguinal lymph nodes are small, firm, discrete and freely movable. Several small nodes are palpable in the right axilla. The abdominal cavity contains approximately 4000 ccs. of yellowish, slightly cloudy, watery fluid which has a specific gravity of 1.014. The peritoneum is thin, moderately injected and lusterless.

The mesenteric lymph nodes at the root of the small intestine are enlarged, firm and elastic in consistency forming a nodular, bulky, circular mass approximately 16 cms. in diameter (Fig. 2). The individual nodes range from 1 to 5 cms. in diameter, are discrete and sharply outlined against the surrounding mesenteric fat. Their capsules are thickened and dense but there is no tendency toward fusion or adhesions. One of the larger nodes contains a circular cyst at one pole 2 cms. in diameter filled with some yellow, oily fluid and pasty, thick, yellow, grumous material. Elsewhere its cut surface as well as that of the remaining nodes sectioned is smooth and homogenous ranging from light yellowish-grey to pale tan in color. The peripncreatic and adjacent periaortic nodes show similar but less marked enlargement. The serosal surface of the gastro-enteric tract is dull and lusterless but free of adhesions. Small vessels are moderately dilated. Examination of the mucosa of the entire gastro-enteric tract reveals no noteworthy gross abnormalities.

The slate blue spleen weighs 100 grams and is covered by a thin wrinkled capsule. Multiple sections show a

purplish-red firm surface in which follicular and trabecular markings appear normal.

The tannish-brown liver weighs 1270 grams and is covered by a thin, smooth capsule. Cut sections are dull, pale brown and finely streaked with occasional yellow zones. The vascular and lobular markings appear normal. The gall bladder is thin-walled and contains approximately 60 ccs. of golden-brown viscid bile. The bile passages are patent and of normal calibre. The pancreas is greyish-white, firm, and of average consistency and outline.

The kidneys together weigh 335 grams and are of normal size and cut appearance. The mucosa of the pelvis and ureters is smooth, greyish-white, and glistening. The thin-walled urinary bladder contains approximately 260 ccs. of urine and presents a white trabeculated mucosa.

The tests are present in the scrotal sac and present no gross abnormalities.

The suprarenals are of normal size and outline, and on section exhibit light tan cortices and soft, dark grey medullae. A few dense fibrous lesions are present over the left upper and middle lobes of the lung. 300 ccs. of straw-colored, watery fluid is present in the left pleural cavity and 200 ccs. in the right. Multiple sections of both lungs reveal purplish-red, moist surfaces, irregularly mottled with small, firm, darker greyish-purple zones. The mucosa of the bronchial tree is red and lusterless; the hilic lymph nodes are small and firm.

A thick, shaggy, partly fibrous grey exudate binds the



Fig. 3. Jejunum x160. Diffuse mucosal infiltration of fat-laden foam cells and scattered extracellular fat droplets with penetration below muscularis mucosa.



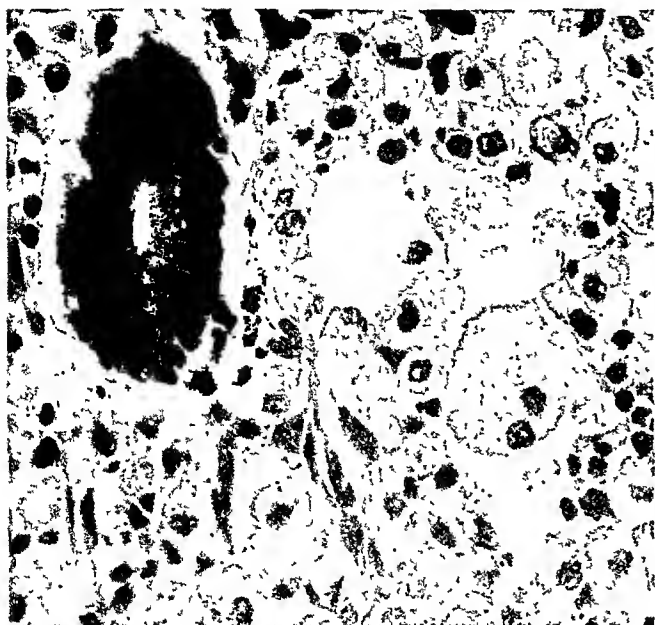


Fig. 4. Jejunum x600. Irregular coarse fat droplets within the mononuclear cells of the mucosa and extracellular fat droplet.

epicardium firmly to the inner surface of the pericardial sac. The valvular endocardium is generally thin and transparent except for the anterior cusp of the mitral valve which shows some slight thickening and opacity at the free edge. The chordae tendineae are thin, smooth and glistening. The myocardium is of normal appearance and the coronary vessels present no noteworthy changes. The non-dilated, tortuous, inelastic aorta exhibits a moderate number of yellowish intimal plaques throughout the abdominal and thoracic portions. The brain was not examined because of autopsy restrictions.

Microscopic sections taken from various levels of the jejunum and ileum show the mucosal villi markedly widened and blunted by a diffuse granulomatous reaction which extends a short distance into the submucosa (Fig. 3). Outstanding cytologically are great numbers of closely packed large mononuclear cells averaging about 3 to 4 times the diameter of a red blood cell. The nuclei are small, dark, round to kidney-shaped, and for the most part moderately off center. The cytoplasm is abundant and mottled with irregularly fine to coarsely granular, pale droplets which appear to vary considerably in size within the individual cell (Fig. 4). Irregularly placed between these foamy mononuclear cells are large clear spaces which have the usual appearance of free fat droplets stained by hematoxylin and eosin. In a few areas these spaces are provided with endothelial lining cells and give the impression of dilated lymph capillaries. Bordering some are one or more multinucleated foreign body giant-cells. Sprinkled sparsely between the bulky foam cells are small groups of polymorphonuclear neutrophils, small lymphocytes, and occasional plasma cells. Stromal blood capillaries are uniformly engorged and moderate diapedesis of red cells is present. Some old blood pigment lies within phagocytic cells. The extensive cellular infiltrate separates and partially distorts the Lieberkuhn's crypts of the mucosa. Scattered vacuoles are contained beneath the free border of their columnar lining cells. An occasional crypt is cystic, its lining epithelium flattened and atrophic. The submucosa is markedly edematous and widened. That portion just below the muscularis mucosa is involved in an extension of the lipohagic granulomatous reaction noted in the mucosa. Here also are dilated endothelial-lined lymph channels containing clumps of mononuclear foam cells. Solitary lymph follicles and Peyer's patches are distributed normally throughout the small bowel but

no germinal centers are seen. The muscle coats are regular. Some thickening of the serosa is due to a sub-serosal deposition of connective tissue infiltrated with fibroblasts, lymphocytes and polynuclear cells. Blood capillaries are dilated and numerous. All the coats of the duodenum are intact for a distance of 1 cm. below the pyloric ring. Beyond this point are scattered clusters of foam cells in the mucosal stroma which become progressively larger and fused as the jejunum is approached. The colon appears essentially intact.

Foot and Foot silver impregnation of sections of the jejunum and ileum demonstrate a delicate reticulum enveloping individual large mononuclear foam cells within the mucosa and submucosa. Giemsa and acid-fast stains show no bacteria. Sections from several widely separated areas in the stomach show a slight reduction in the number and size of the mucosal glands. The supporting stroma is correspondingly thickened and infiltrated with small lymphocytes, plasma, and occasional polynuclear cells. A few glands are cystic. The serosa is thickened by a small amount of non-specific granulation tissue. Lymph nodes of the enlarged mesenteric groups exhibit typically a sponge-like pattern with great numbers of large round, clear spaces throughout cortex and medulla lined for the most part by flattened endothelial cells. Close to their periphery are scattered large multinucleated giant-cells, in some areas completely encircling the circumference (Fig. 5). Occasional dilated lymph channels within the enveloping, thickened, fibrous capsules appear to communicate with some of these spaces. Large foamy mononuclear cells of the type noted in the intestinal mucosa, scattered fibroblasts, polymorphonuclear eosinophiles and neutrophils are seen. Stained with Scarlet Red and osmic acid, the large clear spaces as well as the cytoplasm of the foam cells and some of the multinucleated giant-cells give the typical reaction for neutral fat (Fig. 6). Examination with polarized light shows occasional small anisotropic granules in some of the large fat droplets. The development of a fine reticulum about individual mononuclear foam cells is demonstrable with silver stains. Some of the nodes show thick, patchy, fibrous scars replacing the parenchyma. Levaditi method yields no organisms. Chemical examination showed no essential difference between the lymph node fat and samples taken from the adjacent mesentery. In both, the iodine numbers and phospholipid content were that of normal depot fat.

There is some fibrous thickening of the splenic capsule and condensation of the pulp reticulum. Follicles are for

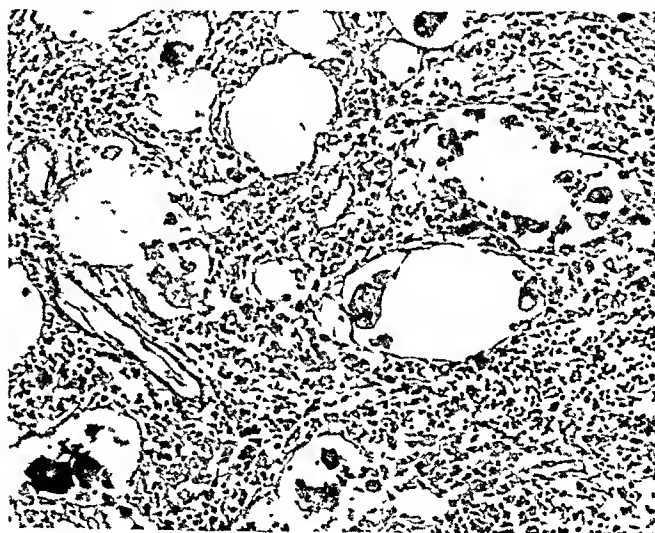


Fig. 5. Mesenteric lymph node. Dilated endothelial lined spaces filled with fat and surrounded by multinucleated foreign giant-cells.

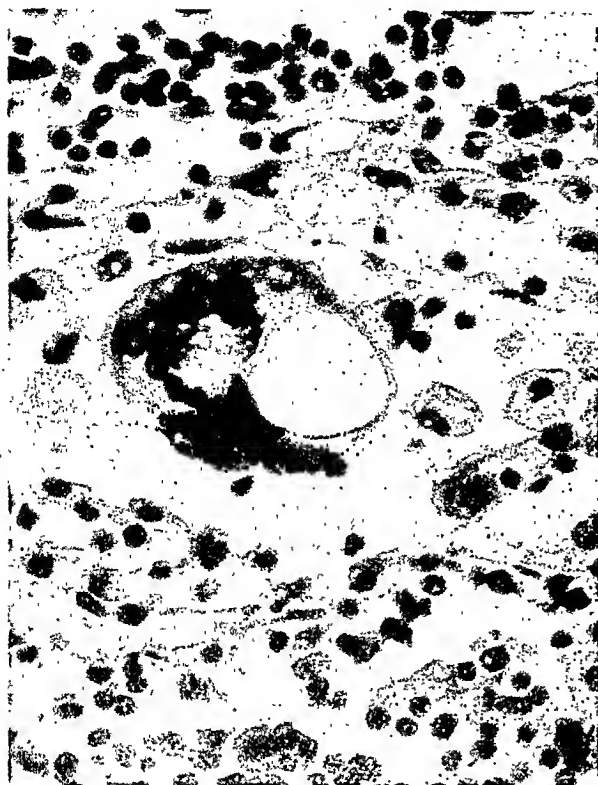


Fig. 6. Mesenteric lymph node  $\times 600$ . Multinucleated giant-cell containing large fat droplet and surrounding foam cells.

the most part well preserved. Endothelial cells lining the sinus reticulum are prominent. No enlarged mononuclear or foam cells are found.

Some passive congestion is seen about the central veins of the liver with slight fatty infiltration. Moderate infiltration of small lymphocytes present in the portal connective tissue. No abnormalities of the Kupffer cells or infiltration of foam cells is present. The epicardium is covered with a thick layer of organizing and partially fibrosed non-specific granulation tissue. No Aschoff bodies or other evidence of rheumatic fever are found. There is a slight fibrous connective tissue increase of the inter- and intralobular supporting tissue of the pancreas. Some of these show infiltration of small groups of small lymphocytes and a few large monocytes. Similar lymphocytic cuffing is present about some of the small blood vessels. The islet tissue is intact. Rarely a few pancreatic acini are replaced by large neutral fat cells. No changes are noted in the epithelium of the ducts. There is slight atrophy of the seminiferous tubules of the testes with some thickening of the supporting membrane.

#### PATHOLOGICAL DIAGNOSES

Lipophagic granulomatosis of the small intestine with massive infiltration of the regional mesenteric, peripancreatic, and periaortic lymph nodes. Ascites. Bilateral hydrothorax. Diffuse organizing pericarditis. Acute bronchopneumonia. Interstitial fibrosis of pancreas (slight). Pleural adhesions. Chronic atrophic gastritis. Slight atrophy of testes. Slight arteriosclerosis of aorta.

#### DISCUSSION

The case described here as well as those reviewed lack sufficient characteristic well defined symptoms, physical signs, or laboratory data that would group

them together as a distinct clinical entity despite the similarity of the essential pathologic changes. The majority appear to be patients in late middle life who suffer from epigastric discomfort, fullness, or bloating, progressively severe asthenia and weight loss, with or without an accompanying diarrhea or steatorrhea. A previous history of polyarthritis was present in less than half of the cases. Progressive secondary anemia appears the rule but the tendency towards lymphocytosis noted in several cases is by no means constant. The hypomotility and stasis of the small bowel with the moulage sign noted on X-ray in our cases can hardly be considered diagnostic (15).

The pathologic changes are characteristically confined to the inner coats of the jejunum and ileum with massive infiltration and enlargement of the draining mesenteric and adjacent peripancreatic lymph nodes. However, there appears to be considerable variation in the degree of small bowel involvement. In several cases reviewed the lesions were minimal or lacked entirely the characteristic features common to the mesenteric nodes. Studies on the fate of lipophagic granulomas elsewhere in the body demonstrate that spontaneous resorption of the free or engulfed fat droplets is not uncommon and marked regressions in the cellular architecture occur (16). Such reversible changes might conceivably have taken place in the intestine without any appreciable change in the lymph node reaction. The sensitivity of the latter to X-ray therapy is of therapeutic interest following the observations of Fleischman and Boeck. The means by which lipophagic granulomas are formed within the small intestine and regional lymph nodes is obscure. Whipple originally suggested that the fat might be in some way abnormal, or that it held some abnormal or toxic substance in suspension. His evidence for this was the abnormally low saponification number of the analyzed lymph node fat, the peculiar foreign body type cellular response to the fat particles, and the presence of numerous ecchymoses and blood pigment suggesting some action on capillary walls. In addition, the pathologic changes were limited to the structures concerned with absorption of fat while the lymphatic tissues elsewhere were relatively normal. He believed a lack of pancreatic lipase unlikely in view of the normal appearance of that gland.

Korseh postulated a functional alteration of pancreatic lipase secretion whereby the intestinal fat content is abnormally split and the absorbed abnormal products provoke a foreign body response in the intestinal mucosa. In support of this theory he held the altered iodine number and freezing point of the lymph node fat and variation in its staining reaction to several standard dyes as evidence of some chemical abnormality. Further the lipogranulomatous reaction appeared to follow the procession of absorbed fats along the lymphatics to the draining mesenteric lymph nodes and to a less extent involved some of the mediastinal nodes.

The presence of a mechanical obstruction along the thoracic duct causing stasis and backflow of chyle in both intestinal lacteals and lymph node sinuses with a resulting granulomatous reaction could not be demonstrated in either of the 2 cases in which careful



dissection was performed. It appears theoretically possible, however, that lymphatic obstruction might be consequent to increased secretion of fat into the lacteals via the blood stream. This overflow would account for the striking dilatation of lymph vessels which appears to be constantly present in both small intestine and the draining lymph nodes. Increased secretion of fat takes place physiologically from excessive mobilization of depot fat, as occurs during starvation, with periodic but enhanced wastage into the blood stream (17). Conceivably more marked, prolonged increases of the wastage fat would cause excess dilution and over-crowding of the mucosal lacteals with inspissation of fat particles and dilatation of the lymph channels resulting in a phagocytic foreign body cellular response. The effects of various endocrine hormones on fat mobilization have been described but their relation to the changes noted here are speculative.

The presence of steatorrhea in the cases reviewed is variable but examinations in many instances have been incomplete. Under normal fasting conditions a certain proportion of wastage fat is excreted into the bowel. Sufficient excess to be classified as steatorrhea should depend on quantitative studies rather than on crude gross estimates. The color change caused by small quantities of blood as noted in our case, can easily divert suspicion of excess fat content. Such repeated loss of red cells through capillary diapedesis appears responsible for the anemia, although nutritional intake may also be a factor.

The presence of the abnormally reduced blood proteins in our case can be explained on reduced food ingestion, or possibly on the basis of impaired intestinal absorption of protein through an altered mucosa.

The pathologic differentiation of lipophagic granulomas of the enteric tract from the generalized lipoidosis appears clearly defined. In the former, the distribution of the lesion is confined to the small intestine and draining mesenteric lymph nodes. Large mononuclear foam cells laden with fat droplets varying considerably in size, and extracellular fat, either free or surrounded by multinucleated foreign body giant-cells, are conspicuous. Further, there is no generalized participation of reticulo-endothelial cellular elements in the process and chemical examination of the lipoidoses show characteristic chemical differences in the lipid content.

### SUMMARY

1. Lipophagic granulomas are defined histologically and cases involving the enteric tract are abstracted from the literature.

2. An additional case is reported occurring in a 45 year-old male who was observed clinically for a period of more than 2 years and the autopsy findings are presented.

3. The pathogenesis and biologic behavior of enteric lipophagic granulomas are briefly discussed to-

gether with their differentiation from the lipid granulomas.

### REFERENCES

1. Bartsch, G. H.: Über Lipophage Granulombildungen (im besondern der Weiblichen Brustdrüse). *Arch. f. klin. Chir.*, 178:62, 1933.
2. Makai, Endre: Über Lipogranulomatosis Subcutanea. *Klin. Wochenschr.*, 7:2313, 1928.
3. H-rbitz, H. F.: Lipogranuloma-Foreign Body Inflammation Often Suggesting Tumor. *Acta Chir. Scand.*, 76:401, 1935.
4. Fleischman, R.: Über tumorbildende Fettgewebsgranulome im Gekrose des Dünndarms. *Arch. f. klin. Chir.*, 158:692, 1930.
5. Vannucci, D. und Montagnana, C.: Lipophages Granulom Infolge von traumatischer Fettgewebsnekrose. *Beiträge zur klin. Chir.*, 161:177, 1935.
6. Bartsch, G. H.: Über Lipophage Granulome. *Beiträge zur klin. Chir.*, 165:487, 1937.
7. Stulz, E. et Fontaine, R.: Le Granulome Lipophagique du Sein. *Revue de Chir.*, 61:646, 1923.
8. Whipple, G. H.: A Hitherto Undescribed Disease Characterized Anatomically by Deposits of Fat and Fatty Acids in the Intestinal and Mesenteric Lymphatic Tissues. *Bull. Johns Hopkins Hospital*, 17:382, 1907.
9. Blumgart, H. I.: Three Fatal Adult Cases of Malabsorption of Fat. *Arch. Int. Med.*, 32:113, 1913.
10. Jarcho, S.: Steatorrhea with Unusual Intestinal Lesions. *Bull. Johns Hopkins Hospital*, 59:275, 1936.
11. Bagen, J. A., Bollman, J. L. and Kepler, E. J.: The Diarrhea of Pancreatic Insufficiency. Discussion by W. C. Boeck. *Am. J. Dig. Dis. and Nutrit.*, 4:728, 1938.
12. Korsch, H. J.: Fettstoffwechselstörung mit Granulombildung im Mesenterium. *Zentralbl. f. allg. Path. u. Path. Anat.*, 71:337, 1938.
13. Hill, J. M.: Mesenterie Chyladenectasis. *Am. J. Path.*, 13:267, 1937.
14. Reinhart, H. L. and Wilson, S. J.: Malabsorption of Fat (Intestinal Lipodystrophy of Whipple). *Am. J. Path.*, 15:483, 1939.
15. Kantor, John: Further Experience with the Roentgen Diagnosis of Idiopathic Steatorrhea. *Arch. Int. Med.*, 65:988, 1910.
16. Abrikossoff, A. I.: Ueber des Schicksal der Spontan Auftretenden Fettgranulome (Lipophagen Granulome). *Verhandl. d. deutsch. Path. Gesellsch.*, 21:57, 1929.
17. Frazer, A. C.: Fat Absorption and Its Relationship to Fat Metabolism. *Physiol. Rev.*, 20:561, 1940.

### DISCUSSION

DR. JOHN L. KANTOR (New York City): Mr. President, Ladies and Gentlemen: I wonder whether lipophagic granulomatosis is associated with steatorrhea resulting from defective fat absorption. If this is so it is possible that the small intestine will show the so-called "moulage" pattern, that is, an abnormally smooth outline due to ironing out the valvulae conniventes. This appearance is, however, best revealed in films taken one or two hours after the administration of a standard barium meal. To wait for 5½ hours before making this observation, as I believe was done by the authors, is too long for the best results as most of the meal has left the jejunum by that time.

In all cases in which steatorrhea may be present, quantitative studies of the fecal fat are very helpful, as well as investigation of the pancreas function during life, and section of this organ post-mortem. Did the authors have an opportunity to make these tests?

If it should appear to be true that there is difficulty in absorbing fat in lipophagic granulomatosis, then this condition must be added to the list of the other diseases characterized by "idiopathic" steatorrhea, namely, sprue, endemic and tropical, eelie disease, lymphosarcoma of the intestine, lymphosarcoma of the mesenteric lymph nodes and tuberculous mesenterica (tuberculosis of the mesenteric lymph nodes).

Finally, may I ask the members of this Association to let me know of cases that exhibit the "moulage sign." I shall be very grateful for such information.

DR. SEATON SAILER (Cincinnati, Ohio) (closing the discussion): As to the studies of the stool for quantitative fat, only one examination was made and this was reported as within normal range.

The pancreatic changes consisted of slight interstitial fibrosis which appeared insufficient to cause any alteration in the physiology of the gland.

## Ileocolostomy with Exclusion for Non-Specific Ileitis

By

RALPH COLP, M.D., JOHN GARLOCK, M.D.

and

LEON GINZBURG, M.D.  
NEW YORK, NEW YORK

**I**N the following communication the authors report their experience with the operation of ileocolostomy with exclusion in the treatment of distal regional ileitis. Although, like most other surgeons, they started with little regard for the procedure as a final form of therapy, the excellent results following its application as the first stage of a contemplated two stage resection necessitated a revision of their original views.

As the results of resection in localized types of the disease have been satisfactory, it might be asked why any other procedure should be advocated. The answer involves the important question of mortality. It is true that one-stage ileocecal resections may be performed in the uncomplicated variety of the disease with an attendant low operative mortality. However, formidable difficulties due to adhesions to neighboring viscera and the abdominal parietes, and the presence of fistulae may tax the skill of the most experienced surgeon. Ileocolostomy with exclusion is an indirect effective and simpler procedure. In such cases, it obviates the necessity for widespread dissection with the possibility of injury to adjacent and often densely adherent viscera. It avoids extensive raw areas as sites for further adhesions and possibly intestinal obstruction. The possibility of peritonitis from accidental opening of encapsulated purulent foci is also reduced. It can be carried out with a negligible mortality by the surgeon who only rarely encounters the disease. In the forty cases herewith reported there has been no operative mortality and no serious post-operative complications.

The objections raised against ileocolostomy with exclusion are largely on a priori grounds. These may be grouped under three headings: first, that undesirable mechanical and physiological conditions might supervene; secondly, that healing would fail to occur in the excluded diseased loop; and thirdly, that the continued presence of a primarily diseased segment of ileum would favor the extension of the pathological process to proximal segments previously uninvolved. The validity of these objections will be examined in the light of our experience with forty such cases.

1. Mechanical and physiological effects following ileocolostomy with exclusion.

The objection has been raised that the transected and inverted end of distal ileum might "blow out" because of obstruction occurring in the diseased loop. We have never encountered this complication either in the present series of cases or in numerous other cases in which this surgical maneuver was carried out. The reasons for this are quite obvious. When one re-

members that complete stenosis in regional ileitis, is rare, it will be seen that recession of the inflammatory edema which usually follows the side-tracking procedure permits ready egress of the small amount of mucoid secretion in a distal direction.

An objection frequently voiced is that retrograde passage of stool into the excluded proximal colon and cecum would produce stasis, distention, and possible ulceration. On numerous occasions, barium was given by mouth and the opaque material was seen to pass retrogradely as far as the cecum. However, emptying occurred within forty-eight hours in practically every instance. Furthermore, during the course of secondary operations, we have never noted any abnormality in the excluded segment of colon.

Another objection to the operation of ileocolostomy with exclusion is that diarrhea might follow the implantation of a loop of ileum into a distal segment of colon. That this not infrequently occurs cannot be denied. It must be pointed out, however, that an effective ileocolic resection just as frequently produces the same result. Dissatisfaction with the shortcircuiting procedure is, in large measure, due to the failure of differentiating between entero-colostomy in continuity and entero-colostomy with exclusion. In our opinion, the necessity of complete exclusion by dividing the ileum proximal to the disease has not been stressed sufficiently. When this part of the procedure is omitted, only partial diversion of the fecal stream is obtained. Under such circumstances, the diseased bowel will not be put at complete rest, and perforations may occur and fistulae will continue to discharge. The trapping of fecal material between the new stoma and the diseased segment of bowel might cause further trouble. Estes and Holmes have called attention to the fact that such a loop itself may be the cause of new and severe symptoms. We have seen this on two occasions.

2. The healing effect on the diseased loop of ileocolostomy with exclusion. 39 cases. (No follow up in one case).

This procedure becomes doubly effective in a type of disease in which the tendency for spontaneous healing is already present. That such a tendency exists in regional ileitis is evidenced by the marked fibro-plastic granulomatous reaction seen in the bowel wall. Putting the bowel at rest and completely diverting the infectious fecal stream seems to favor the separation process. The same apparently does not hold true following shortcircuiting operations in the treatment of segmental ulcerative colitis.

The necessity for complete diversion of the fecal stream in order to facilitate healing has been emphasized. However, there is a small group of cases in

\*From the Surgical Services of The Mount Sinai Hospital, New York, N. Y.

Read at the Annual Meeting of the American Gastro-Enterological Association at Atlantic City, N. J., May 6, 1942.

which this ideal result cannot be obtained. These are the cases in which the primary ileal disease is complicated by the presence of ileosigmoidal fistula. In such instances the stasis of stool and gas in the rectum results in retrograde passage of some of this material into the communicating diseased ileal loop. Sufficient infectious material may thus enter other fistulae and sinuses and keep the inflammatory process active. Our experience with this operation in two such cases has been unsatisfactory. These patients not only did not show transient improvement, but continued to undergo progressive deterioration. However, it should be stated that in both instances the physical condition of the patient was so poor, and the pathological process so extensive that resection was out of the question. In addition to these two cases, either persistence or recurrence of the disease in an affected loop necessitated secondary resection in *three other cases*, a total of five, a failure incidence of approximately 15%. If, however, the two cases mentioned above, representing a type of ileitis for which the shortcircuiting operation is unsatisfactory, are excluded, the failure percentage drops to approximately 8%. In other words, in approximately 90% of the cases the results have been highly satisfactory.

What evidence is available to support the contention that healing occurs in the excluded loop? In three instances secondary resections performed for various reasons showed definite and conclusive evidence of healing. In another case in which an autopsy was performed on a patient dying of other causes, similar findings were demonstrated. In two patients, operative inspection of the previously excluded loop showed unmistakable evidence of regression and healing as compared with the original findings.

In the remaining cases the beneficial effects of the operative procedure as judged by the subsequent improvements in the clinical course were quite apparent.

(1) Fever. In patients who ran prolonged febrile course, subsidence of fever resulted within a few weeks.

(2) Enteritic symptoms. The relief of severe enteritic symptoms was complete in many instances at the time of discharge from the hospital. In some patients the stools became solid in consistency after a few months. In others, the frequency of bowel movements, without cramps or dyschesia, continued despite marked improvement in all other aspects. This phenomenon, however, has also been encountered following resection with enterocolostomy in the treatment of other diseases. Persistence of severe enteritic symptoms or their recurrence after a free interval was found to be due to proximal extension of the disease in two instances, and re-activation of disease in the excluded loop in one. The cause in the latter was probably due to extension of inflammation from the diseased excluded loop, to the sigmoid to which it was adherent.

(3) Obstructive symptoms. These were invariably relieved by shortcircuiting operations.

(4) Fistulae. In seven out of eight cases of abdominal fecal fistulae, purely ileal in origin, the discharge ceased and the fistulae closed spontaneously. In one instance, recurrent intermittent mucoid discharge persisted. In one case in which a large ileosigmoidal fistula communicated with an external abdominal fecal

fistula, fecal material continued to drain through the fistula.

(5) In all but the two cases of persistent disease recorded above, the inflammatory masses regressed rapidly. In thin individuals, small, non-tender residual masses could at times be palpated, after all symptoms had subsided.

(6) Nutrition and anemia. The marked improvement in the general nutrition was universal. Some of the patients showed a weight gain of fifty to sixty pounds. Even in the two patients in whom there was recurrence of disease in the excluded bowel, this improvement in nutrition was marked. There was usually a marked improvement in the blood picture, with an increase in hemoglobin.

3. Relation of proximal extension of regional ileitis to the type of primary operation.

Before discussing this phase of the problem it should be pointed out that recurrence of symptoms following a shortcircuiting procedure is not necessarily due to reactivation of disease in the excluded loop. It may also be due to involvement of a proximal segment of bowel previously apparently normal. Such proximal extension has been noted following resection as well as exclusion.

When operations for regional ileitis were first being undertaken, a certain number of cases of supposedly new proximal involvement were undoubtedly due to over-looked diseased segments at the time of the primary operation. At that time the significance, frequency, and extent of "skip areas" were not understood. With the careful exploration which is now being undertaken, this type of proximal "extension" will probably become less frequent.

Another point which we have learned with increasing experience, is to divide the ileum further proximally than we formerly did. In distal ileitis it is not uncommon for two to three feet of normal bowel to be included in the shortcircuited segment. It is important to emphasize that the reason for this precaution is that there are considerable variations in the stage and degree of pathological alteration of different segments of the bowel in the same case. Usually, there is a diminution in the severity of the process in an oral direction. Experience has shown that the bowel just proximal to the last grossly visible area of disease might appear normal at the time of operation, but show definite evidences of disease a short time later.

In the opinion of some authors, proximal extension of the disease is more apt to occur following a shortcircuiting operation than after resection. The excluded loop of bowel is regarded as a focus from which extension takes place along the mesenteric lymphatics. Our observations do not support this contention. We have already shown that the overwhelming number of excluded segments of bowel undergo healing. In addition, we have observed such new proximal disease only once in this series of ileocolostomies, and in that patient there was a "skip area" of about three feet. Incidentally, in a parallel series of resections, such proximal extension was encountered three times in thirteen cases. This relatively greater frequency following resection is probably accidental. On the other hand there is the possibility that in resection there may be a tendency to divide the bowel too close to the diseased site because of the understandable reluctance on the part of the surgeon to

resect a large segment of apparently normal bowel.

That the condition of the excluded loop is not the determining factor in the involvement of proximal segments is suggested by the following experiences. In the one case of ileo-colostomy in which this sequel occurred, the excluded loop was found healed and the new area of disease was situated about three feet proximal to the stoma. In another case, a secondary resection was performed on a patient for recurrent symptoms. The excluded loop of bowel was resected in spite of the fact that there was no evidence of active disease, and it was shown by pathologic examination to be the seat of a healed lesion. The region of the stoma and the bowel proximal to it were carefully explored and appeared to be normal. Eight months later definite radiological and operative evidence of disease was found in the segment of bowel beginning at the anastomosis and extending proximally for a distance of a few feet. On the other hand in the three cases of persistent disease in the excluded loop, no such complication occurred, although one of these patients continued to harbor the inflamed segment for ten years.

These experiences would indicate that the deciding factor in the prevention of post-operative proximal disease is not what is done to the primary diseased segment. Performance of the resection or exclusion at a level high enough to allow for the clinically not demonstrable, but possibly present disease seems to be much more important. It is important to note that this entire discussion is centered about the treatment of distal ileitis. In cases in which such distal ileitis is complicated by proximal, localized, jejunal involvement, it would probably be wiser to resect the proximal lesion, re-establish continuity at that point, and exclude the distal segment. Cognizance must also be taken of the fact that there are cases of jejuno-ileitis which are not susceptible to surgical treatment by either method. In these, sufficiently radical therapy in either case would result in the failure to leave sufficient functioning small bowel to adequately perform the functions of digestion and absorption.

#### SUMMARY

1. A series of 40 cases of regional ileitis treated by ileo-colostomy with exclusion is reported.

2. There were no operative mortalities nor any serious post-operative complications.

3. 40 cases were available for follow-up studies. There was recession of disease in the excluded loop in 35.

4. The above five failures include two cases complicated by a large ileo-sigmoidal fistula. In this type of case the operation is ineffective and cannot be expected to offer satisfactory results. If this type of case be excluded, the ratio of unsuccessful cases is 3 out of 38.

5. Appearance of disease in proximal segments previously uninvolved occurred in 1 case.

6. Proximal extension of the disease appears to be independent of the type of operation used to treat the primary lesion.

7. The important factor in preventing such extension appears to be to carry the site of exclusion or resection sufficiently oral.

#### DISCUSSION

DR. BURRILL B. CROHN (New York City): Further progress on the subject of enteritis and ileitis will rest in

the hands of surgeons; it is in the field of surgery where, at present, the greatest differences of opinion arise.

It is of interest to see the splendid results of the operation of short-circuiting as reported by Dr. Colp. His absence of mortality is of great moment. In a more general group of cases collected from surgeons in an earlier series, mortality for primary resection and short-circuiting was approximately 10%, a not inconsiderable death rate. Perhaps the earlier cases were more severe because they were recognized later or because the course of the disease had been prolonged before recognition. Early diagnosis and prompt action will undoubtedly lead to a lower mortality and a better handling of the situation.

My early preference was always for the primary resection; I felt that the short-circuiting operation left in situ the inflammatory mass which retarded the recovery of the patient. On the other hand, it is frequently striking to see how such an inflammatory mass can resolve after a short-circuiting procedure. I recall a mass the size of a fetal head, which, after a short-circuiting operation became, in the post-operative convalescence, so reduced that it could no longer be felt. Rectal fistulas often close up after a short-circuiting operation.

The divergence of opinion among surgeons still exists as regards a one- or two-stage procedure. Certainly the current of opinion seems to be veering toward a short-circuiting operation. In addition, it is beginning to be realized that the second stage of the operation may often be dispensed with; the second operation has often disclosed the fact that the lesion was practically healed, and that the second-stage operation could have been avoided.

Recently, I saw, for the first time, a case of ileitis with obstruction, a necrotic, gangrenous mucosa. In this instance resection was absolutely mandatory and the immediate result was good.

Apparently the question of recurrences is independent of the type of operation, whether resection or short-circuiting. I can agree with Dr. Colp that the question of recurrences depends upon the ability to recognize skip areas. How these skip areas are to be recognized I am not sure. Apparently there is a great deal of difficulty in palpating or in observing beginning inflammatory lesions which are so small that they escape detection. At the early stage when the lesion is mucosal or submucosal, and before an inflammatory granulomatous reaction has taken place, it is practically impossible for a surgeon to observe and identify such early lesions. Under the circumstances the only safe procedure is to resect excessively high.

Dr. Brown objects to the use of the word "well," after operation for ileitis. A very large proportion of the cases are well and stay well following successful operative approach. In that respect, ileitis is different from peptic ulcer or ulcerative colitis, and I feel that a case of ileitis, once well, a case that stays well for more than a year, will probably remain cured for a life-time.

I have seen no beneficial effects from sulfanylguanidine in cases of ileitis. Not only is it disappointing, but it seems to cause irritation and a rise of temperature.

DR. H. NECHELES (Chicago, Ill.): I want to tell about some experiments that Dr. Kozoll, one of my associates, has done in relation to the surgical treatment of colitis.

We performed short-circuiting operations on the intestines of dogs and follow-up with fluoroscopy and X-rays. The distal ileum was implanted into the middle of the colon. Following a barium-meal meal by mouth, we observed that the short-circuited part filled up rather regularly, but also emptied regularly and quickly as the barium progressed in the colon. Of course, the short-circuited part of the ileum was normal, and we feel that in the rigid, pathological, short-circuited ileum this might not happen, but that the danger of stasis may occur.

The second series of experiments was done on patients

and on animals in order to find a drug which would overcome the diarrhea and increased motility of the small and large intestines following extensive resections and short-circuiting operations. We found that opium, atropine, and pituitrin were not of much avail, but that one of the newer drugs, an ester of diphenyl-amino acetic acid, sold under the trade name of Trasentin, was beneficial in a number of patients. One patient who had had most of his small intestine resected and had about twenty bowel movements a day, was able to reduce those to one to two, and also to reduce the dose of the drug, so that he was able to go back to work.

DR. HENRY L. BOCKUS (Philadelphia, Pa.): Mr. President and Guests: I am from Philadelphia, and it is with great timidity that I stand here to comment on these many cases from New York and Rochester, Minnesota. I have not seen hundreds of cases, nor have I seen cases in the forties, but I have personally studied and followed 14 cases before and after operation. I have seen approximately twenty-five additional cases.

Dr. Crohn referred to Dr. Colp's low mortality. Dr. Colp didn't have any mortality. He had forty cases without a death. Unfortunately, we have not been so successful—we have had two deaths in our 14 cases. Our first death followed what was intended to be a two-stage resection for an advanced ileocolitis. The ileum was not transected, and that is one of the main points that I should like to make in this discussion. We are convinced that, because of experience with four cases, if a two-stage operation resection is contemplated, the ileum proximal to the lesion must be transected. If this is not done, further extension of the lesion will be found at the time of the second-stage procedure. It is because of this finding of extension of the lesion following the first stage that I am unable to understand Dr. Colp's results, and I am quite willing to accept the figures which he has given, having had no experience with the side-tracking operation. I wish we could report similar results. The thing that is difficult for me to understand is how this disease with its extensive involvement of the mesentery in advanced cases can be cured permanently by any procedure short of removal.

Possibly Dr. Monaghan is in the room. He can refute Dr. Crohn's argument that late recurrences do not occur. We had occasion to observe the end results of a patient who had an operation for this lesion four years before Dr. Crohn's first paper appeared. The description by the pathologist in the Methodist Hospital in Philadelphia was almost word for word your description, Dr. Crohn. An ileo-transverse-colostomy with resection had been performed. Twelve years later Dr. Monaghan had this patient at the Bryn Mawr Hospital with a recurrent involvement of a foot and a half of the terminal ileum proximal to the transverse colostomy.

A one-stage resection has resulted in a lower mortality than the two-stage resection in our series. We have found in our own cases that the longer the interval between the operation and the follow-up, the more recurrences we have had. Our first three cases, six and a half years, six years and five years respectively after operation have experienced recurrences. It is very difficult to exclude the presence of a recurrence on clinical evidence alone since the patients may stay comparatively well for a long time. The only way to be sure is through very frequent follow-up studies with progress meal and barium enema studies. If this plan was universally adopted, I am confident that recurrences in this disease, regardless of the type of operation, would be found to be relatively frequent. However, these patients may go on for years and die of some other disease, which undoubtedly they do, just as in ulcerative colitis. The more acute process may burn itself out, and what is left is only the inert pathology with very little active infection.

DR. LEON GINZBURG (New York) (closing the discussion): Mr. President and Gentlemen: I would like to

illustrate some of the points brought out by Dr. Colp in the paper and get some further details on the follow-up before you.

(Slide) This is the operation of ileocolostomy in continuity without division of the loop, the operation which we do not do and which we think is a very poor operation. In the first place, a considerable quantity of intestinal material will pass by the stoma and will continue to pass this infectious material over the ulcerations and continue to discharge from the various fistulae. In the second place, rigidity and fibrosis in a diseased loop may give rise to stasis between the stoma and that loop, with subsequent ulceration, not due to disease but to stasis occurring here.

Holmes and Estes have produced such ulcerations experimentally in animals.

(Slide) This is the operation which we do perform. There is complete division of the ileum and closure with an enterocolostomy. I think a very important point is to carry this division far enough proximally. I think the more or less unsatisfactory results which were achieved early in the game, in our knowledge of the disease, were to some extent due to the fact that the division was carried out too close to the diseased area.

In looking over some of our sections in the pathological laboratory, it was often noted that this was no more than six inches away. Today it is not uncommon for us to perform this division at three feet from the last visible area of disease in distal ileitis.

Dr. Crohn said he didn't know how you could tell when you had reached it. You can't, absolutely, but I have found a good way is to hold the bowel up against the light, and when the intestinal contents show through translucently, you are beginning to get to fairly healthy bowel.

As far as the follow-up is concerned, of the thirty-three cases in whom we have favorable results as far as the excluded loop is concerned, we have followed eighteen of these for more than three years and fifteen three years or less, and of those eighteen, five have been for nine years or more.

So far as the time of recurrence is concerned—and I call this reappearance of disease in this segment—recurrence and reappearance here, extension or progression—we had two cases of ileosigmoidal fistula complicating the ileitis, and there was no improvement whatsoever either local or general. In one case there was failure of a fistula to heal at all, even though there was marked general improvement. A third case was well for three years and gained fifty pounds in weight, and then had to be reoperated because of the development of an abscess in the mesentery of excluded bowel, due to perforation of an ulcer on the mesenteric side of the bowel between the leaves of the mesentery. That was three years after the operation. The other case recurred within a year after operation, also had done very well, gained weight, and in this patient there was a real segmental reactivation, and it was interesting to note that in the resected specimen there were no new areas of disease. We had excluded about two feet of normal bowel with the diseased bowel and the reactivation had occurred in exactly the same segment as previously.

As far as proximal extension of the disease is concerned, in this series we have had one case, and that was a boy in whom the original operation was done for fistulae, and the bowel was transected about six inches proximal to the last visible area of disease. This was done about twelve years ago. Within six months he had reappearance of the disease in the proximal segment, not at the stoma but about three feet proximal to it. Resection done at that time was followed by a disappearance of symptoms, to date.

DR. PHILIP W. BROWN (Rochester, Minn.) (closing the discussion): Of course, the only way that we can help these people who have this serious disease is by the discussions such as we have had this morning, and none of



us is particularly trying to champion a cause. We are all fighting for the same end and that is to aid the person who is sick.

Now, there is no question in these people that have recurrence of the disease, whether it is recurrence in a segment that is left, or in a skip area that was overlooked at the time of surgery, and if it is then necessary to undertake another resection, the results are unfortunate in most instances. As I pointed out, there are only four of that group that we would consider as well. I am

perfectly willing to consider them well and I hope with all my heart that they are well.

I feel that Dr. Bockus is perhaps a little pessimistic that the majority of them may get into further trouble. I don't think that is quite as good an outlook as our experience has been, and I do hope, though, that there will be someone in this group or some allied group, who is going to get in and do some good, serious work, from the pathologic standpoint and from the standpoint of study of tissue itself.

## A Clinical Study of the Secretin Test<sup>\*†</sup>

By

H. M. POLLARD, M.D., LILA MILLER, Ph.D.

and

W. A. BREWER, B.A.

ANN ARBOR, MICHIGAN

**A** TEST of the functional capacity of the pancreas has been one of the needs of medicine. Theoretically, secretin should serve as the basis for such a test. However, an available, non-toxic preparation of secretin was lacking until after the hormone had been crystallized as the picolonate in 1933 (1). While the cost of this crystalline product was prohibitive for clinical use, Hammarsten and his group isolated in a similar manner, though with less extensive purification, an amorphous product which was non-toxic and which had one-tenth to one-twentieth the activity of the secretin derived from the crystalline picolonate.

The results obtained by Ågren and Lagerlöf (2) with this amorphous secretin indicated abnormal function of the pancreas in cases of acute and chronic pancreatitis and in cases of carcinoma of the pancreas, which seemed to be related to the mass of active tissue in the gland. Furthermore, the cholagogic effect of this secretin which was free of cholecystokinin offered another opportunity to test the functional capacity of the gall bladder.

As with all new tests, evaluation can be made only after clinical studies have been reported by a number of different groups. Only within the last 3 or 4 years has the commercial preparation<sup>‡</sup> been available in the United States. Hence, studies of the usefulness of this test in this country have been limited (3, 4, 5).

One objection to the test as originally described (6) is the length of time required for the participation of the subject and for the analyses. In the second place, the methods used for the determination of the reducing sugars in the estimation of the amylase activity and for the conversion of the titration values into units of trypsin might well be modified for convenience and accuracy.

In this paper are presented the results obtained with the secretin test as applied to 33 individuals with a shorter period of collection of the digestive juices and with modified analytical procedures.

### EXPERIMENTAL

After the subjects had fasted for 12 hours, the double lumen gastro-duodenal tube was placed in position and checked fluoroscopically. To decrease unpleasant sensations which may attend the swallowing of the tube, a 2 per cent solution of pontocain was applied to the throat in the form of a spray. The specimens of gastric juice and the combined duodenal and pancreatic juices were withdrawn continuously but separately in the manner similar to that described by Ågren and Lagerlöf (6). Four consecutive collection periods followed the intravenous administration of the secretin, the first two of 10 minute duration and the last two of 20 minute duration. Thus the total time of collection was 20 minutes less than that used by Ågren or by Diamond and his group in their first work (2, 3).

In all cases the dose of the secretin was 1 clinical unit per kilogram of body weight.

### ANALYTICAL PROCEDURES

All the specimens were centrifuged to remove the cellular debris. To calculate the quantities of bicarbonate and enzymes secreted, the volume of the clear supernatant liquid was used. All determinations of pH were made with a glass electrode.

**Bicarbonate.** The titration method of Van Slyke (7) was adapted to the concentrations encountered in the juices by the use of 0.1 N solutions of sulfuric acid and sodium hydroxide. To facilitate sharper endpoints, the solutions were boiled after they had been treated with the acid, shaken 1 minute and diluted with carbon dioxide-free water.

**Trypsin.** The trypsin activity was determined by the Willstätter method in the modified form used by Ågren and Lagerlöf (6). However, instead of the alcoholic solution of potassium hydroxide, an aqueous 0.1 N sodium hydroxide was employed for this titration without a significant sacrifice of accuracy as the volume of the water at the end of the titration did not exceed 10 per cent.

The unit for trypsin defined by Willstätter (8) was too large for the quantities encountered in the juices. Furthermore, the relation between the titration

\*This work was done under a grant from the research funds of the Horace H. Rackham School of Graduate Studies.

†Presented before the Central Society of Clinical Research, Chicago, Illinois, November 5, 1940.

‡Pancrestatin, Astra, Södertälje, Sweden.

From the Department of Internal Medicine and Biological Chemistry of the University of Michigan Medical School, Ann Arbor. Submitted June 12, 1941.

‡Winthrop Chemical Company.

values and the units devised by Ågren and co-workers did not appear reasonable. Therefore to set up a unit, a number of paired activity determinations were made with 1 and 2 cc. of the same juice. (The concentration of water in the digestion mixtures was maintained by the omission of 1 cc. of water when 2 cc. of the enzyme solution were used). To the data from 8 experiments, the rule of Schütz was applied:

$$x = k \sqrt{E}$$

$x$ , being the protein hydrolyzed measured in terms of cc. 0.1 N sodium hydroxide;  $k$ , a constant; and  $E$ , the units of enzyme. If that quantity of enzyme which effected a hydrolysis equivalent to an increase in titration of 0.250 cc. 0.1 N sodium hydroxide is chosen as one unit,  $k$  is equal to 0.25. Then by the use of this value for  $k$ , the units were calculated for each titration. It was then possible to compare the observed values and those calculated for twice the concentration of duodenal-pancreatic juice. The greatest difference between the observed and the calculated values by this method was +11 per cent with an average of +9.5 per cent, whereas deviations of -38 to +16 per cent were obtained when the system of units used by Ågren and Lagerlöf was applied to these data.

**Amylase.** The procedure Somogyi (9) devised for the amylase activity of blood was employed for the estimation of the amylase activity of the digestive juices. However, as a matter of convenience, a temperature of 30° C. rather than 40° was employed for the juices. For blood, the diastatic activity is expressed as mg. of glucose, produced by the enzymatic activity of 100 cc. of blood. Therefore, for the duodenal-pancreatic juices a similar system has been used, the reducing substances, expressed as mg. of glucose produced by the action of 1 cc. of the juice under the standardized conditions.

**Bile Pigments.** The Meulengracht method was applied to the duodenal-pancreatic juices in a manner similar to that for the icteric index of serum (10).

The method was unsatisfactory if little dilution was required as it was then difficult to match the specimen against the dichromate standard in the colorimeter.

All gastric samples were examined with respect to pH and titratable acidity. If regurgitation had occurred, these samples were analyzed in the same manner as the duodenal-pancreatic juices and the data thus obtained included with that for the corresponding duodenal-pancreatic specimen.

In general the analytical results have been expressed on the basis of the body weight—i.e., the amount secreted after the stimulation by secretin per kilogram of body weight. However, for the sake of comparison, the maximum concentration of bicarbonate has been given.

## RESULTS

Two types of subjects made up the control group for which the data are presented in Table I. Group A consisted of patients who were being treated in the hospital for some condition unrelated to gastro-intestinal diseases, and Group B of healthy medical students leading an active life.

Obviously eight cases are an insufficient number to warrant average values. Therefore, the minimal and maximal values given in the table constituted the standards for judging the pathological cases. The anomalously low value for the maximum concentration of bicarbonate in Case 27 seemed sufficient reason for omission from the minimal value presented for bicarbonate concentration. However, the total secretion calculated as millicquivalent per kilogram for this subject is within the range of the whole group.

Table II includes the subjects diagnosed as having some organic disease of the pancreas. Those cases which presented clinical evidence of carcinoma of the pancreas comprise Group A. The diagnosis of carcinoma was confirmed by operation or autopsy in all instances except Case 7. In five (9, 19, 22, 24, 39) of

TABLE I

Analytical data of duodenal-pancreatic juices obtained from individuals free of gastro-intestinal diseases following injection of secretin

| Case              | Volume Per Kg.<br>of Body Wt. | Maximum<br>pH | Bicarbonate              |                        | Trypsin Per Kg.<br>of Body Wt. | Amylase Per Kg.<br>of Body Wt. |
|-------------------|-------------------------------|---------------|--------------------------|------------------------|--------------------------------|--------------------------------|
|                   |                               |               | Maximum<br>Concentration | Per Kg. of<br>Body Wt. |                                |                                |
|                   | cc.                           |               | m. eq.<br>per l.         | m. eq.                 | Units                          | Units                          |
| A*                |                               |               |                          |                        |                                |                                |
| 2                 | 1.3                           | 9.18          | 89                       | 0.08                   | 1.0                            | 325                            |
| 4                 | 1.9                           | 8.47          | 106                      | 0.13                   | 13.2                           | 2,029                          |
| 6                 | 0.7                           | 9.06          | 141                      | 0.08                   | 2.0                            | 833                            |
| 33                | 2.0                           | 8.61          | 100                      | 0.15                   | —                              | 2,848                          |
| 34                | 2.1                           | 8.43          | 114                      | 0.15                   | 6.1                            | 1,594                          |
| B*                |                               |               |                          |                        |                                |                                |
| 27                | 2.6                           | 7.42          | 39                       | 0.08                   | 2.5                            | 2,570                          |
| 28                | 2.1                           | 8.55          | 107                      | 0.10                   | 2.6                            | 1,573                          |
| 32                | 1.4                           | 8.11          | 75                       | 0.10                   | 3.1                            | 774                            |
| Minimal<br>values | 0.7                           | 7.42          | 75                       | 0.08                   | 1.0                            | 325                            |
| Maximal<br>values | 2.6                           | 9.06          | 141                      | 0.15                   | 13.2                           | 2,848                          |

\*Groups A and B include hospitalized individuals and medical students, respectively.



TABLE II

Analytical data of duodenal-pancreatic juices obtained from individuals with diseased pancreas following injection of secretin

| Case | Volume Per Kg.<br>of Body Wt. | Maximum<br>pH | Bicarbonate              |                        | Trypsin Per Kg.<br>of Body Wt. | Amylase Per Kg.<br>of Body Wt. |
|------|-------------------------------|---------------|--------------------------|------------------------|--------------------------------|--------------------------------|
|      |                               |               | Maximum<br>Concentration | Per Kg. of<br>Body Wt. |                                |                                |
|      | cc.                           |               | m. eq.<br>per l.         | m. eq.                 | Units                          | Units                          |
| A**  |                               |               |                          |                        |                                |                                |
| 7    | 1.9                           | 8.78          | 94                       | 0.14                   | 1.2                            | 276                            |
| 9    | 0.5*                          | 8.29          | 105                      | 0.03*                  | 0.8*                           | 320*                           |
| 19   | 1.4                           | 8.70          | 82                       | —                      | 8.1                            | 717                            |
| 21   | 0.7                           | 8.39          | 91                       | 0.13                   | 2.9                            | 1,440                          |
| 22   | 1.6                           | 8.10          | 20*                      | 0.03*                  | 0*                             | 127*                           |
| 24   | 0.2*                          | 8.28          | —                        | —                      | 5.5                            | 204*                           |
| 39   | 0.2*                          | 7.78          | —                        | 0.003*                 | 0*                             | 4*                             |
| B**  |                               |               |                          |                        |                                |                                |
| 23   | 2.0                           | 8.54          | 116                      | 0.20*                  | 1.2                            | 709                            |
| 25   | 2.3                           | —             | 124                      | 0.22*                  | 5.7                            | 1,114*                         |
| 26   | 2.2                           | 8.29          | 87                       | 0.15                   | 15.7*                          | 1,636                          |

\*Indicates an abnormal value on the basis of the control group.

\*\*Groups A and B include those cases of neoplasms of the pancreas and those tentatively diagnosed as chronic pancreatitis, respectively.

†Bicarbonate was determined on the pooled specimens because of the limited amount of secretion.

the seven cases, the carcinoma was located in the head of the pancreas. The data for all these except Case 19 were distinguished by a low total secretion of one or both the enzymes, a low bicarbonate secretion, and for Cases 9, 24 and 39 the volume was diminished. The apparently normal volume of the juices for Case 22 was the result of impaired function of the gall bladder. Since the head of this gland has been demonstrated to be the most active part for the secretion of the digestive juice, the observed diminished secretion was to be expected (11). In Case 19, which did not fall in line with the others, the location of the carcinoma had been established by an operation a year prior to this secretin test and by autopsy two months later. The fact that this woman was seven months pregnant when the test was performed may be significant.

The two remaining cases, 7 and 21, did not show the distinctive abnormalities noted above. In Case 7 the amylase was low, whereas in Case 21 all data were

within the range of the control group. The data for these two cases were in conformity with the final diagnoses, of an abdominal neoplasm or lymphoblastoma for Case 7, and for Case 21 of a retroperitoneal carcinoma in the region of the pancreas found by laparotomy. Thus carcinoma of the head of the pancreas appears to cause a diminution in the secretion of both bicarbonate and the enzymes, whereas carcinoma in other parts of the gland or in the region of the gland is not clearly reflected in the composition of the pancreatic secretion.

Group B of Table II consists of those cases tentatively diagnosed as chronic pancreatitis. Case 25 may be eliminated since this patient's complaints were finally attributed to a psychoneurosis subsequent to and independent of this secretin test. The only deviation of the data for that case was a high bicarbonate secretion which could not be attributed to impaired function of the gall bladder. In the other two cases an elevated secretion of bicarbonate was the chief

TABLE III

Analytical data of duodenal-pancreatic juices obtained from individuals with severe diabetes mellitus following injection of secretin

| Case | Volume Per Kg.<br>of Body Wt. | Maximum<br>pH | Bicarbonate              |                        | Trypsin Per Kg.<br>of Body Wt. | Amylase Per Kg.<br>of Body Wt. |
|------|-------------------------------|---------------|--------------------------|------------------------|--------------------------------|--------------------------------|
|      |                               |               | Maximum<br>Concentration | Per Kg. of<br>Body Wt. |                                |                                |
|      | cc.                           |               | m. eq.<br>per l.         | m. eq.                 | Units                          | Units                          |
| 5    | 2.1                           | 8.46          | 111                      | 0.18*                  | 2.0                            | 1,286                          |
| 10   | 0.4*                          | 8.75          | 129                      | 0.02*                  | —                              | 127*                           |
| 11   | 0.7                           | 7.69          | 36*                      | 0.01*                  | 19.1                           | 100*                           |
| 13   | 0.4*                          | 8.72          | 62*                      | 0.04*                  | —                              | 557                            |
| 15   | 0.5*                          | 8.59          | 65*                      | 0.02*                  | 5.4                            | 491                            |
| 16   | 1.9                           | 8.19          | 97                       | 0.13                   | 2.0                            | 254                            |

\*Indicates an abnormal value on the basis of the control group.

deviation and these patients had poorly functioning gall bladders. The lack of definitely pathological results with this pancreatic functional test in the cases diagnosed as chronic pancreatitis on the basis of pain, vomiting or thickening of the head of the pancreas at operation is in agreement with the observations of the Swedish workers who found only 1 definitely pathological secretion out of 11 supposed cases of chronic pancreatitis (2).

A simultaneous chronic disturbance of the internal and the external secretions of the pancreas is considered a rarity. Therefore, no pathological deviations of the secretin test in the cases of diabetes mellitus were anticipated. However, a diminished output of bicarbonate characterized four (10, 11, 13, 15) of the six cases presented in Table III, and a low volume characterized three of these four. Thus these two factors appear to be associated with each other and may be related to hypoplasia of the non-cretory tissue. The rather high volume and bicarbonate observed in Case 5 might be the result of the continuous biliary drainage into the duodenum, which would tend to increase both these factors. In Case 16 no abnormalities whatsoever were present. In the literature there have been reported two cases of diabetes mellitus in which a low bicarbonate secretion occurred following the administration of secretin, and the data for the volumes in these instances were not given (4).

Abnormalities in the enzyme content of the juices in these cases were few. In Case 10 a low amylase content was observed and in Case 11 a high trypsin accompanied the low amylase.

In Table IV 7 cases of severe long-standing chronic cholecystitis and cholelithiasis and a single case of carcinoma of the gall bladder are presented as Group A, and cases of choledocholithiasis as Group B.

In Group A distinct abnormalities were not present other than the elevated volumes in Cases 17 and 20, and the increased trypsin content in Cases 26 and 31. The large volume in Case 17 could not be attributed

to the failure of the gall bladder to take up the bile as in Case 20. The two instances of elevated tryptic activity may point to a possible association of a pancreatic disturbance and disease of the gall bladder. The absence of disturbances in the secretion of bicarbonate and amylase was distinctive for this group of subjects in contrast to the other pathological cases.

Of the 2 cases in Group B, Table IV, Case 3 was thought to have a common duct stone on the basis of clinical symptoms though no history of jaundice, nor of acholic stools was presented. The results from the secretin test resemble those for Group A in the same table. Apparently the stone did not seriously obstruct the common duct since hepatic bile continuously drained into the duodenum as the result of a cholecystectomy. This presence of biliary drainage due to the absence of a gall bladder could explain the large volume. Likewise, in Case 8, the gall bladder was not present at the time of the test. Therefore, the absence of a large volume of secretion and the borderline character of the bicarbonate secretion in conjunction with the obvious jaundice of the patient pointed to a marked common duct obstruction. Two days after this secretin test, a large stone was removed from the ampulla of Vater.

The data for the relative concentrations of bile pigments are presented in Table V in 4 groups. In the cases in Group A, at least one colorless duodenal-pancreatic specimen was obtained after the administration of the secretin. This condition was indicative of the presence of a functioning gall bladder and contrasted with the presence of bile in all specimens where no gall bladder was present. In two cases grouped under B, contraction of the gall bladder apparently had occurred prior to the administration of the secretin and the complete absence of bile in the last sample was considered evidence of storage of bile in the gall bladder at the end of the experiment. In Group C, bile was present in all the specimens after

TABLE IV

Analytical data of duodenal-pancreatic juices obtained from individuals with suspected gall bladder disease following injection of secretin

| Case | Volume Per Kg.<br>of Body Wt. | Maximum<br>pH | Bicarbonate              |                        | Trypsin Per Kg.<br>of Body Wt. | Amylase Per Kg.<br>of Body Wt. |
|------|-------------------------------|---------------|--------------------------|------------------------|--------------------------------|--------------------------------|
|      |                               |               | Maximum<br>Concentration | Per Kg. of<br>Body Wt. |                                |                                |
|      | cc.                           |               | m. eq.<br>per l.         | m. eq.                 | Units                          | Units                          |
| A**  |                               |               |                          |                        |                                |                                |
| 14   | 2.0                           | 8.31          | 87                       | 0.15                   | 4.5                            | 928                            |
| 16   | 1.9                           | 8.19          | 97                       | 0.13                   | 3.0                            | 910                            |
| 17   | 4.3*                          | 8.10          | 82                       | 0.16                   | 3.3                            | 2,660                          |
| 18   | 1.7                           | 8.61          | 110                      | 0.10                   | 1.8                            | 956                            |
| 20   | 3.3*                          | 7.99          | 79                       | 0.14                   | 11.1                           | 1,516                          |
| 26   | 2.2                           | 8.29          | 87                       | 0.15                   | 15.7*                          | 1,056                          |
| 31   | 1.3                           | 8.15          | —                        | —                      | 21.0*                          | 975                            |
| 40   | 1.3                           | 8.62          | 77                       | —                      | 1.5                            | 469                            |
| B**  |                               |               |                          |                        |                                |                                |
| 3    | 3.0*                          | 8.30          | 85                       | 0.10                   | 6.8                            | 741                            |
| 8    | 1.3                           | 8.58          | 122                      | 0.05*                  | —                              | 417                            |

\*Indicates an abnormal value on the basis of the control group.

\*\*Groups A and B include the cases diagnosed cholecystitis, cholelithiasis, or both, and the cases of choledocholithiasis, respectively.

the administration of the hormone, whereas in Group D bile pigments were absent in all specimens.

The agreement between this phase of the test and the clinical records for the cases in Groups A and B was good. Of the 11 cases, the records of 4 contained no reference to the gall bladder, 3 were marked "Gastro-intestinal system history was entirely negative," and 2 showed normal visualization of the gall bladder by the choleystogram. Two instances of lack of agreement between the secretin test and the X-ray of the gall bladder (Cases 16 and 24) were observed. The X-ray of the former had been taken 8 months

prior to this test and the latter had had jaundice for 3 weeks.

In Group C, as in Groups A and B, the functional capacities of the gall bladder as indicated by this test and by the case record were similar. For 6 of the cases no reference to biliary diseases was in the case histories. Of the remaining cases, 3 and 8 had a cholecystectomy sometime prior to the secretin test; hence continuous drainage should have occurred. X-ray records which were available for the remaining 11 cases of this third group indicated that for 8 of these there was a partial or complete non-visualization

TABLE V

Content of bile pigments as estimated by the Meudengracht number in duodenal-pancreatic juice prior to and following injection of secretin.

| Case | Period* |       |       |       |       |       |
|------|---------|-------|-------|-------|-------|-------|
|      | 1       | 2     | 3     | 4     | 5     | 6     |
| A    |         |       |       |       |       |       |
| 2    | 83      | 84    | 143   | 0     | 0     | +     |
| 6    | 40      | +     | 124   | 0     | 0     | 272   |
| 13   | 332     | 107   | +     | +     | 0     | 146   |
| 16   | 0       | 0     | 0     | 0     | 478   | 855   |
| 17   | +       | +     | 0     | 0     | 0     | 22    |
| 24   | +       | +     | +     | +     | +     | 0     |
| 25   | —       | 127   | 104   | 0     | 0     | 0     |
| 27   | 216     | 241   | +     | 0     | 0     | 64    |
| 28   | 178     | 15    | +     | 0     | 0     | 41    |
| B    |         |       |       |       |       |       |
| 10   | 2,187   | 3,502 | 5,194 | 77    | +     | 0     |
| 19   | 2,973   | +     | 3,675 | 631   | 167   | 0     |
| C    |         |       |       |       |       |       |
| 3    | +       | +     | 2,018 | 903   | 1,031 | 1,241 |
| 4    | +       | +     | 2,208 | 1,421 | 521   | 1,446 |
| 5    | 656     | 669   | 3,898 | 5,517 | 2,601 | 1,174 |
| 7    | +       | +     | 1,351 | 66    | 1,724 | 1,534 |
| 8    | —       | 579   | 6,568 | 76    | 87    | 189   |
| 9    | 82      | 258   | 622   | 1,605 | 3,435 | 120   |
| 11   | +       | 596   | +     | 833   | 1,912 | +     |
| 14   | —       | —     | 323   | 283   | 992   | 373   |
| 15   | +       | 512   | 310   | 210   | +     | +     |
| 18   | +       | 135   | 173   | 23    | +     | 140   |
| 20   | +       | 0     | 495   | 35    | 98    | 3,100 |
| 21   | +       | 4,004 | 1,455 | +     | 419   | 4,597 |
| 22   | 533     | 1,109 | 1,529 | 862   | 2,453 | 1,648 |
| 23   | 1,035   | 1,859 | 1,002 | 217   | 750   | 1,290 |
| 26   | 2,301   | +     | 1,367 | 2,146 | 2,653 | 1,360 |
| 31   | 301     | 4,273 | 7,092 | 1,400 | 4,737 | 2,997 |
| 32   | 499     | 351   | 495   | +     | 620   | 3,686 |
| 36   | 130     | 37    | 3,056 | +     | 1,493 | 1,760 |
| 40   | +       | +     |       |       |       |       |
| D    |         |       |       |       |       |       |
| 39   | 0       | 0     | 0     | 0     | 0     | 0     |

\*Periods 1 and 2 were of 20-minute duration and prior to the administration of the secretin. Periods 3 and 4, the first two following the administration of the secretin, were 10 minutes, whereas periods 5 and 6 were 20 minutes.

0 indicates a water clear sample; +, the presence of pigments which could not be estimated due to a low concentration or a low volume; and —, the absence of secretion.

of the gall bladder, and normal visualization for the remaining 3 cases. However, in these 3 cases the periods elapsing between the date of the secretin test and the X-ray was 5 days, 7 weeks and 8 months, respectively. Thus in only one case was there a complete disagreement between the two methods of testing the function of the gall bladder.

In the single case listed as Group D there was a complete absence of bile pigments in all the duodenal-pancreatic samples. Thus it is similar to the observations reported by Ågren and Lagerlöf (12) for the case of complete exclusion of hepatic and gall bladder bile. However, those cases were characterized by low but constant concentrations of bile pigments rather than by a complete absence of the pigments. This patient was jaundiced at the time the secretin test was performed. Ten days later a carcinoma of the head of the pancreas was found at operation. Therefore, the complete obstruction may have been caused by the carcinoma.

This agreement between the secretin test and the case records is further evidence of its value both as a double functional test for the pancreas and the gall bladder as has been reported (3, 4, 12).

### DISCUSSION

The secretin test applied in a slightly modified manner yields in the pathological cases studied results similar to those obtained by others (2, 3, 4, 12, 13). Where the mass of the active tissue of the pancreas was diminished as in carcinoma of the head of the gland, a diminution in the secretion of bicarbonate and of one or both the enzymes, amylase and trypsin, was observed. In some of these cases the interpretation of the volume of secretion obtained from the duodenum was complicated by biliary drainage. Cases of cholecystitis and cholelithiasis of long standing failed to show by this test any marked disturbances of the pancreas.

This agreement between our results and those of others makes it evident that the shorter period of collection in no way affects the value of the test. Likewise, the modifications of the analytical procedures do not change the gross results. Furthermore, to present the data for the bicarbonate as the total amount secreted in a given period rather than its concentration is a better manner of expression since the concentration may be characteristic of the normal secretion while the total bicarbonate secreted over a

given time interval may be abnormal. Case 10, Table III, is an instance of this situation.

Diminished response to secretin has been previously reported in only two cases of diabetes mellitus (4). The consistent results in four out of the six cases in our group is of importance. The other group which showed distinct abnormalities included the cases of carcinoma in the head of the pancreas. The disturbances in the former group appear to be chiefly: (1) low volume, and (2) low concentration and total secretion of bicarbonate. In contrast with these results, the juices of the latter group appear to be characterized by a normal concentration but low total secretion of bicarbonate, and by a diminished enzyme content. The number of cases in each group is insufficient for a definite conclusion that these differences are characteristic. The results are, however, very suggestive and warrant further study.

### SUMMARY

1. Thirty-three subjects were used for a clinical study of the effects of injecting purified secretin (Astra). Of these, eight were free of any gastro-intestinal diseases; the others had neoplasms of the pancreas, severe diabetes mellitus, chronic cholecystitis, chronic cholelithiasis, choledocholithiasis, or had been diagnosed as chronic pancreatitis.

2. The procedure of Ågren and Lagerlöf was modified by the use of a shorter period of collection. Both the analytical procedures and the calculation of the units for expressing enzymatic activity were also modified.

3. The results obtained for pancreatic secretion were similar to those reported by others: (a) a diminished secretion of the pancreas if the carcinoma was located in the head of the gland, but not when it was in other regions; (b) no marked association of disturbed pancreatic secretion and chronic diseases of the gall bladder.

4. Four out of the six cases of severe diabetes mellitus had distinctly low volumes of secretion plus low concentration and total output of bicarbonate, with some abnormalities in the enzymes.

5. One case with clinical evidence of chronic pancreatitis showed no evidence of disturbed pancreatic function by the secretin test.

6. The stimulating effect of the secretin on the liver proved valuable as a test for gall bladder function. The correlation between these results and the clinical findings was good.

### REFERENCES

1. Hammarsten, E., Ågren, G., Hammarsten, H. and Wilander, O.: Versuche zur Reinigung von Sekretin. V. *Biochem. Z.*, 264: 275-284, 1933.
2. Ågren, G., Lagerlöf, H. and Berglund, H.: The Secretin Test of Pancreatic Function in the Diagnosis of Pancreatic Disease. *Acta Medica Scand.*, 90:224-271, 1936.
3. Diamond, J. S., Siegel, S. A., Grili, M. B. and Karlen, S.: The Use of Secretin as a Clinical Test of Pancreatic Function. *Am. J. Dig. Dis.*, 6:366-372, 1939.
4. Diamond, J. S. and Siegel, S. A.: The Secretin Test in the Diagnosis of Pancreatic Diseases with a Report on One Hundred Thirty Tests. *Am. J. Dig. Dis.*, 7:435-442, 1940.
5. Comfort, M. W. and Osterberg, A. E.: Pancreatic Secretion in Man After Stimulation with Secretin and Acetyl-beta-methylcholine Chloride. *Arch. Int. Med.*, 66:668-706, 1940.
6. Ågren, G. and Lagerlöf, H.: The Pancreatic Secretion in Man After Intravenous Administration of Secretin. *Acta Medica Scand.*, 90:1-29, 1936.
7. Van Slyke, D. D.: Studies on Acidosis, XVIII. Determination of the Bicarbonate Concentration of the Blood and Plasma. *J. Biol. Chem.*, 52:495-499, 1922.
8. Willstätter, R., Waldschmidt, E., Danaiturria, S. and Künstner, G.: Zur Kenntnis des Trypsin, XV. Abhandlung über Pankreasenzyyme. *Z. physiol. Chem.*, 161:191-209, 1926.
9. Somogyi, M.: Micro Methods for the Estimation of Diastase. *J. Biol. Chem.*, 125:399-414, 1938.
10. Meulengracht, E.: Die Klinische Bedeutung der Untersuchung auf Gallenfarbstoff im Blutserum. *Deutsch. Arch. f. Klin. Med.*, 132:285-300, 1920.
11. Voegtlin, W. L., Greengard, H. and Ivy, A. C.: The Response of the Canine and Human Pancreas to Secretin. *Am. J. Physiol.*, 110:198-224, 1934.
12. Ågren, G. and Lagerlöf, H.: The Biliary Response in the Secretin Test. *Acta Medica Scand.*, 92:359-366, 1937.
13. Lagerlöf, H.: The Secretin Test of Pancreatic Function. *Quart. J. Med.*, (new series) 38:115-126, 1939.

# Functional Disturbance of the Small Intestine in Chronic Idiopathic Ulcerative Colitis

By

KENDALL A. ELSON, FRANCIS G. DICKEY

and

FRANCIS W. CHORNOCK

PHILADELPHIA, PENNSYLVANIA

**M**ANY of the late clinical manifestations of chronic idiopathic ulcerative colitis appear to arise from a serious disturbance of the digestive or the absorptive function of the small intestine. The evidence for this is varied. (1) A marked loss of weight and hypoproteinemia frequently develop in spite of a dietary intake known to be adequate. (2) The stools often contain undigested food material the presence of which cannot be attributed to small intestinal hypermotility. (3) The roentgenologic appearance of the small intestine is abnormal in a high percentage of cases (1). (4) Clinical evidence of coexistent deficiency disease is frequent. Pellagra (2), macrocytic anemia, glossitis, cheilitis, peripheral neuritis have repeatedly been described (3). Deficiencies of Vitamins A and C and of prothrombin have been reported by Mackie, Eddy and Mills (4). Defects in dark adaptation due to avitaminosis A are recorded (5). While undoubtedly these deficiency states result in some instances from dietary inadequacy, both qualitative and quantitative, they may occur even though the diet is adequate in all known essentials and suggest the existence of an intrinsic functional defect of the small bowel.

In the present study an attempt was made to gain objective quantitative evidence of this functional disturbance so that a more exact analysis of the factors responsible for it might be made. We have demonstrated a decrease in the absorption of protein by the small bowel in patients with this disease. Subjects whose treatment necessitated ileostomy were placed on a diet of known protein content, and the unabsorbed fraction of the ingested protein in the ileal discharge was measured. In approximately one-half of the subjects an abnormally large amount of the ingested protein was not assimilated. This functional defect was absent after clinical improvement had occurred and is regarded as a result rather than a cause of the disorder. Further analysis of the mechanism underlying it may, it is hoped, yield information concerning factors which influence small intestinal absorption both in health and disease.

## METHOD OF STUDY

Seven patients who had undergone ileostomy for the treatment of idiopathic ulcerative colitis were studied. At varied stages of convalescence they were placed for four days on a diet which consisted of soda crackers and a mixture of milk, cream, eggs, malted

milk, sugar and chocolate. In the quantities voluntarily consumed the diet provided from 69 to 169 grams of protein and approximately 2000 to 4000 calories daily. During the last 3 of the 4 days all food consumed was accurately measured and a daily sample was analyzed for its nitrogen content by the Kjeldahl method. On each of these 3 days all ileal and rectal discharges and urine were collected separately and were analyzed for nitrogen. The nitrogen balance was calculated for each day, the final result being expressed as the average for the 3 day period. If small intestinal hypermotility had previously been observed roentgenologically the time of transit of a small amount of a standard water-barium mixture from the duodenum to the ileal stoma was determined. In one instance (J. F.) atropine sulphate (gr. 1:200 t.i.d.) was administered throughout the first 4 day period.

## RESULTS

The results are summarized in Table I. As the normal standard for nitrogen absorption by the human small bowel we have taken the figures of Welch, Wakefield and Adams (6). These data were obtained from a subject who had undergone an ileostomy because of congenital polyposis of the colon. At operation the small bowel appeared morphologically normal and is assumed to have been functionally normal as well. In this case an average of 86 per cent of the nitrogen consumed during a 3 day period was absorbed. The minimal absorption was 81 per cent, and this we have accepted as the lower limit of normal.

Four of our subjects (G. L., J. S., J. F., W. B.) had what we consider a significant reduction in the digestive and/or absorptive function of the small bowel. They absorbed respectively 50, 64, 76 and 76.5 per cent of the ingested food nitrogen. The figures obtained in the remaining 3 (M. A., L. A., A. K.) were normal, 84, 86 and 87 per cent.

No consistent correlation between deficient protein absorption and such clinical abnormalities as avitaminosis, hypoproteinemia and malnutrition was observed. For example, G. L., whose protein absorption was the lowest of the entire group, had no frank signs of deficiency disease. L. A., on the other hand, had hypoproteinemic edema, neuritis, cheilitis, gingivitis, glossitis, anorexia and serious malnutrition. His protein absorption, however, was normal (86.6 per cent). In the two remaining cases (J. S. and W. B.) with impaired protein absorption obvious signs of a deficiency state were manifested by glossitis, neuritis, hypoproteinemic edema and severe anorexia. In both the latter instances all evidence of avitaminosis

\*From the Gastro-Intestinal Section (Kinsey-Thomas Foundation) of the Medical Clinic, Hospital of the University of Pennsylvania, Philadelphia, Pa.

(The costs of this investigation were defrayed in part by a grant from Smith, Kline and French Laboratories, Philadelphia, Pa.).  
Submitted June 5, 1941.

had disappeared when subsequent observations demonstrated normal protein absorption.

Small intestinal hypermotility could so reduce the time permitted for digestion and absorption as to cause an abnormally large residue of nitrogen in the ileal contents. This, however, was not evident in our observations. In the 4 subjects with decreased protein absorption the small intestinal transit time for barium was normal (7), i.e., over 1 hour and 30 minutes.

In 3 subjects the nitrogen balance observations were repeated after clinical improvement was evident. In 1 instance (J. S.) the protein absorption was very much more complete on the second and third determinations, while in the other 2 cases (W. R., J. F.) a slight increase over the original figure, which was itself almost normal, was obtained on the second test. Whatever process, therefore, is responsible for the decreased absorption of nitrogen, it appears to be reversible.

It will be observed that in all but 2 instances the nitrogen balance was positive, sometimes very markedly so. This is to be expected in a group of subjects who had for months been losing weight to the point of serious malnutrition and who now had begun to gain weight rapidly.

### DISCUSSION

These observations substantiate the clinical data cited earlier which suggest that ulcerative colitis can by no means be regarded as a disease limited to the colon. Evidence from clinical (3) and roentgenological (1) study and the results of absorption studies, both direct and indirect (4, 8), indicate that a significant disorder of the small bowel also exists in approximately one-half of the cases. Since, however, it is irregular in occurrence and a late manifestation it must be considered a result of the disease in the colon rather than its cause.

Welch, Adams and Wakefield (9) observed an abnormally large fecal excretion of nitrogen in 3 cases

of ulcerative colitis. Since the nitrogen excretion was proportional to the severity of the ulcerative process the loss was attributed to an excessive amount of exudate and blood from the surface of the colon. These authors minimized the importance of changes in the character of the small intestine. Our results do not wholly support this conclusion. Although in certain of our subjects the loss of nitrogen in the rectal discharges was excessive, even though diversion of the fecal current by ileostomy probably had minimized the bleeding and exudation by the colon, the fact remains that the nitrogen loss in the ileal discharges was likewise excessive in 4 out of 7 subjects. This can only be the result of small intestinal dysfunction.

The factors responsible for the observed disturbance in function are unknown. Hypermotility of the small intestine, a possible cause, was not present in our cases, though it is sometimes observed in this disease. Edema of the bowel, which might disturb its normal function, appears unlikely in view of the normal concentration of plasma proteins and the absence of edema elsewhere. Disturbances in the gastrointestinal tract are observed in induced Vitamin B complex deficiency (10). The question arises in this connection whether the morphologic changes observed roentgenographically are associated with functional disturbances. Our limited data indicate no relationship between deficient protein absorption and clinical evidence of avitaminosis.

The first step in the further analysis of this problem should be a determination of the extent to which the ingested protein is broken down as it traverses the small bowel. This will demonstrate whether the observed defect is primarily one of faulty absorption of normally digested nitrogenous end products or consists of incomplete splitting of the ingested protein.

### CONCLUSIONS

Nitrogen balance studies have been carried out in 7 severely ill patients with idiopathic ulcerative colitis in whom ileostomy had been performed. The ex-

TABLE I  
Daily nitrogen output (grams)

| Subject<br>Date                                 | Nitrogen<br>Intake<br>(grams) | Urine                 | Ileal<br>Discharge   | Rectal<br>Discharge | Total<br>Output         | Nitrogen<br>Balance<br>(grams) | Small Intestinal<br>Absorption, Per Cent<br>of Nitrogen Ingested |
|---|-------------------------------|-----------------------|----------------------|---------------------|-------------------------|--------------------------------|--|
| Welch et al (9)                                 | 10.28<br>6.50<br>7.10         | 7.52<br>7.70<br>7.31  | 1.37<br>1.19<br>1.33 |                     | 8.89<br>8.89<br>8.64    | +1.39<br>-2.39<br>-1.54        | 96.4<br>81.0<br>81.4<br>86.3<br>av.                              |
| G. L.<br>10/28/40-11/2/40                       | 9.81                          | 6.18                  | 4.93                 | 1.99                | 13.10                   | -3.29                          | 49.7   |
| J. S.<br>5/24-27/39<br>9/22-25/39<br>5/23-25/40 | 11.93<br>13.28<br>11.53       | 5.19<br>9.20<br>10.34 | 4.30<br>2.46<br>2.22 | .94<br>.19<br>.11   | 10.43<br>11.85<br>12.67 | +1.50<br>+1.42<br>-1.14        | 63.9<br>81.4<br>80.7   |
| W. R.<br>1/15-17/39<br>6/18-20/40               | 10.46<br>14.84                | 4.86<br>9.78          | 2.45<br>3.23         | .90<br>.15          | 8.21<br>13.16           | +2.25<br>+1.68                 | 76.5<br>78.2   |
| J. F.<br>11/29/39-12/2/39<br>1/18-22/40         | 11.13<br>15.39                | 8.56<br>7.85          | 2.68<br>2.81         | 1.61<br>.82         | 12.88<br>11.48          | -1.75<br>+3.91                 | 75.9<br>81.1   |
| M. A.<br>1/1-3/40                               | 12.49                         | 5.66                  | 1.97                 | .86                 | 8.49                    | +4.00                          | 84.2   |
| L. A.<br>10/10-12/40                            | 14.80                         | 4.43                  | 1.97                 | .87                 | 7.24                    | +7.56                          | 86.6   |
| A. K.<br>4/24-26/40                             | 15.85                         | 6.27                  | 1.99                 | 1.47                | 9.73                    | +6.12                          | 87.4   |

cretion of nitrogen in the ileal discharge was abnormally great in 4 of them. This is taken to indicate a defect in the digestive or absorptive function, or both, of the small intestine. The defect disappeared after clinical improvement had occurred. This is regarded as an expression of a small intestinal abnormality which results in the development of a deficiency state in many of the more severe cases of this disease. Its irregular occurrence suggests that it is a result rather than a cause of the colonic disease.

### REFERENCES

1. Mackie, T. T. and Pound, R. E.: Changes in the Gastro-Intestinal Tract in Deficiency States with Special Reference to the Small Intestine. *J. A. M. A.*, 104:613, 1935.

2. Barnes, J. M.: Typical Pellagra Syndrome Developing in a Patient with Chronic Ulcerative Colitis While Under H-103 Treatment. *Ann. Clin. Med.*, 4:552, 1925-26.
3. Mackie, T. T.: Ulcerative Colitis: II. The Factor of Deficiency States. *J. A. M. A.*, 104:175, 1935.
4. Mackie, T. T., Eddy, W. H. and Mills, M. A.: Vitamin Deficiency in Gastro-Intestinal Disease. *Ann. Int. Med.*, 14:23, 1940.
5. Lerner, H. H. and Rapoport, H. G.: Biophotometric Studies in 30 Cases of Chronic Ulcerative Colitis. *Am. J. Dig. Dis.*, 6:229, 1939.
6. Welch, C. S., Wakefield, E. C. and Adams, M.: Function of the Large Intestine of Man in Absorption and Excretion. *Ann. Int. Med.*, 58:1095, 1936.
7. Chamberlin, G. W.: The Roentgen Anatomy of the Small Intestine. *J. A. M. A.*, 113:1537, 1939.
8. Mackie, T. T. and Eddy, W. H.: The Clinical Value of Quantitative Vitamin Determinations. *Am. J. Dig. Dis.*, 6:547, 1939.
9. Welch, C. S., Adams, M. and Wakefield, E. G.: Metabolic Studies on Chronic Ulcerative Colitis. *J. Clin. Invest.*, 16:161, 1937.
10. Elsom, K. O'S., Lewy, F. H. and Heublein, G. H.: Clinical Studies of Experimental Human Vitamin B Complex Deficiency. *Am. J. Med. Sci.*, 200:757, 1940.

## Movements of the Pancreas

By

C. ABBOTT BELING, M.D., M.Sc.D., CHARLES FREDERICK BAKER, M.D.

and

W. JAMES MARQUIS, M.D.  
NEWARK, NEW JERSEY

**D**URING the past two years we have had the unusual opportunity to observe two patients with disseminated calcification of the pancreas. After examining numerous films of the pancreas in both cases, we became interested in the occasional variations in

In each patient the pancreas was outlined by disseminated calcific shadows, which permitted a delineation of the size, shape and position of the gland. The most striking feature in both cases was the discrepancy between the position attributed to the pancreas

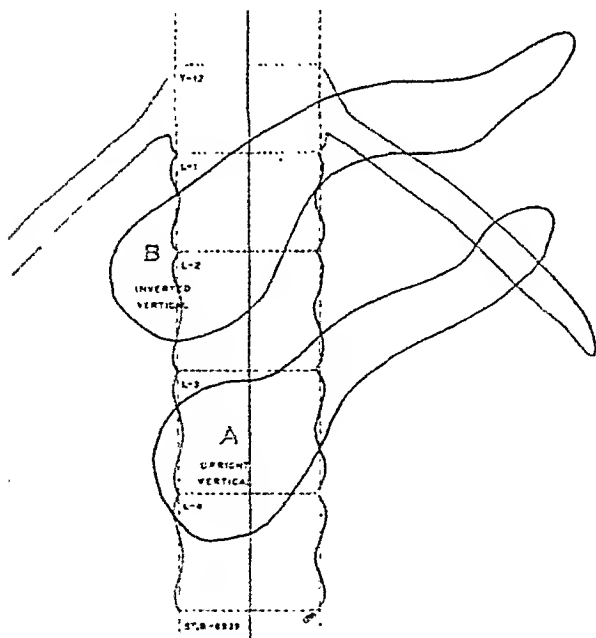


Fig. 1

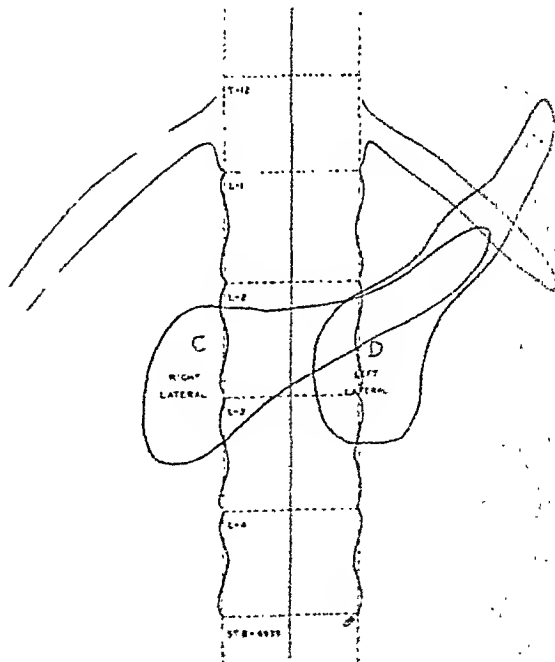


Fig. 2

the location of the organ. Additional roentgenograms were then taken with the patient in various positions to determine if any movement of the organ took place. As far as we know, this is the first time such observations have been made on the pancreas during life.

by anatomy books and the actual position in our films. According to several texts, the pancreas lies at the level of the second lumbar vertebra and extends down over the upper portion of the third lumbar and upward over the lower portion of the first lumbar vertebra. Laterally it is said to extend from slightly to the

\*From the Surgical and Roentgenological Departments of St. Barnabas Hospital, Newark, N. J.  
Submitted June 14, 1941.



right of the spine to the hilum of the spleen in the left hypochondrium. These old anatomic descriptions are based on dissections made on bodies in the horizontal position, these bodies having been in this position for some time preceding death.

We expected the pancreas to be mobile within certain limits, these determined perhaps by its relations with the superior mesenteric vein, which passes upward beneath its lower edge; the superior mesenteric artery and its branches which course over its anterior surface from above; the portal vein, which emerges from behind the superior edge; and the retroperitoneal portion of the duodenum which encircles

We exposed films with the subject in upright and inverted vertical positions and in left and right lateral horizontal positions. By superimposing exactly the films made with the patient in these two different sets of positions and making tracings, we secured Figs. 1, 2, 3 and 4.

Position-A shows the location of the pancreas when a man is standing while B shows where it goes when he is inverted. As one might expect, when a man is lying down the pancreas is midway between the two positions in the location described in the text books. The length of two lumbar vertebrae is the full extent of vertical movement.

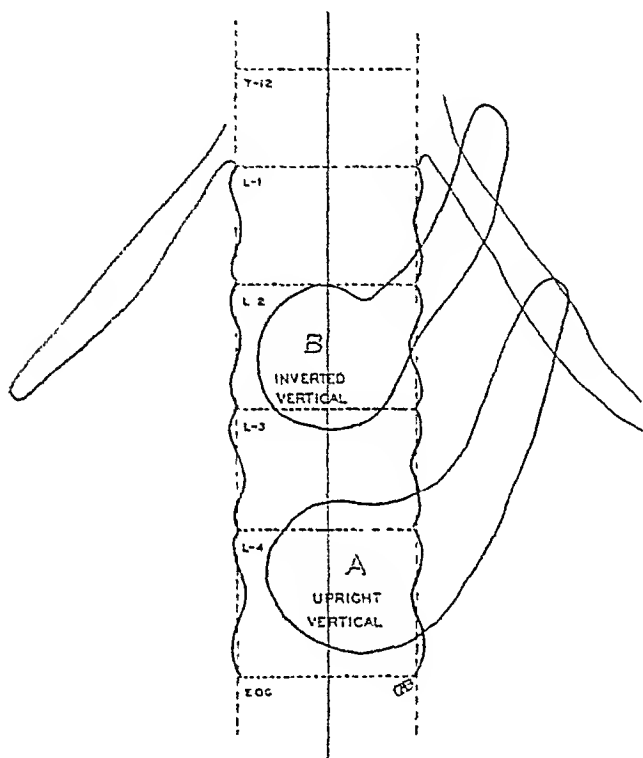


Fig. 3

the head. We know that the position of the duodenum can vary widely with the position of the subject. Movement of the pancreas will be restricted also by its connections with the vena cava and the aorta, the kidneys and the hilum of the spleen. The pancreas does not adhere to these structures except in the median plane and there it is separated from them by loose areolar tissue. It should be remembered that the pancreas originally arose in the mesentery, in embryonic life, and later came into relation with the organs mentioned, being separated from them by two peritoneal layers, one from one side of the mesentery and the other from the posterior peritoneum. These layers fused and the epithelial linings became obliterated.

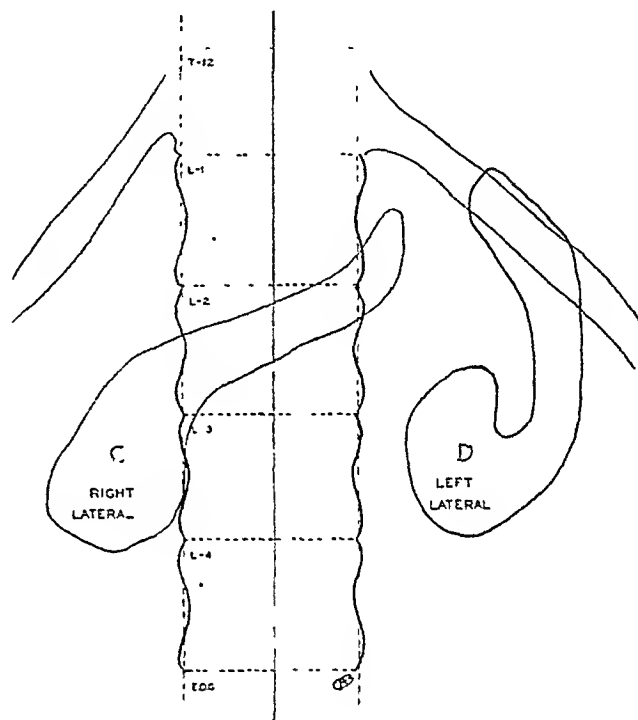


Fig. 4

The other figures show the extent of the lateral movement of the pancreas. As can be seen, it may move completely from the right to the left side of the vertebral column. In the left lateral position the pancreas moves well past the spine and into the left upper abdominal quadrant. In no film did the tail or any other part of the organ rise above the lower border of the eleventh dorsal vertebra.

### SUMMARY

Roentgenograms made of two patients with disseminated calcification of the pancreas placed in several positions show that the pancreas is a mobile organ. The extent of its movements is shown.

## A Case of Atrophic Gastritis Successfully Treated with Liver-Stomach Concentrate\*

By

RALPH U. LESER, M.D.

and

ROBERT J. HASTERLIK, M.D.†

INDIANAPOLIS, INDIANA

THE diagnosis and therapy of that combination of gastric and systemic symptoms now clinically recognized as atrophic gastritis has until recently been relatively unsuccessful. With the elucidation of the gastroscopic picture of atrophic gastritis by Chevalier and Moutier (1), Schindler (2, 3) and others, a firm foundation for the diagnosis of this disease and observation of the effects of therapy is at hand. The case report which follows demonstrates the efficacy of Extralin‡ (liver-stomach concentrate, Lilly) therapy in a patient with chronic atrophic gastritis repeatedly examined gastroscopically.

Jones, Benedict and Hampton (4), demonstrated the reversibility of mucosal changes characteristic of chronic atrophic gastritis accompanying pernicious anemia in induced remissions. Schiff and Goodman (5) recently presented the case histories of five patients with gastroscopic findings of atrophic gastritis not associated with other gastric diseases, pernicious or other anemias, protein deficiency, or obvious vitamin deficiency. Marked symptomatic improvement with a reversal of the gastroscopic findings of atrophy was induced by the oral administration of hog's stomach extract, Ventriculin. This case report concerns a patient with atrophic gastritis without other demonstrable pathology in the gastro-intestinal tract or pernicious anemia.

### CASE REPORT

L. S., a white man of 70 years, entered the Medical Clinic of the Indianapolis City Hospital on August 16, 1939, complaining of gnawing epigastric and peri-umbilical pain appearing about one hour after meals, weight loss of fifteen pounds, anorexia, and constipation. Marked weakness and mental depression were severe and incapacitating features of the illness. "Stomach trouble" had been a distressing problem most of the patient's life.

Physical examination revealed only epigastric and peri-umbilical tenderness and that cachexia usually seen in a patient harboring a carcinoma. Laboratory procedures were essentially non-revealing. An Ewald test meal on August 17, 1939, revealed an achlorhydria, whereas after histamine stimulation, as high as 32 units of free hydrochloric acid were secreted on September 15, 1939. Complete blood counts and blood smears revealed normal findings. Kahn and Kline tests and urinalysis were negative at this time.

Fluoroscopic examination of the upper gastro-intestinal tract appeared negative, but a film made at this time (Fig. 1) revealed what appeared to be a filling defect ap-

proximately three centimeters in length on the proximal one-third of the greater curvature of the stomach. Because of this finding and the symptomatology, the clinical impression was possible carcinoma of the stomach. The patient was referred for gastroscopic examination which on September 6, 1939, revealed typical findings of atrophic gastritis on the lesser curvature and posterior wall in the mid-portion of the stomach and on the posterior wall of its fundus. The large, prominent submucosal blood vessels were a striking feature.



Fig. 1. Apparent filling defect of greater curvature of stomach not confirmed by gastroscopy.

The patient was placed on a modified Sippy dietary regimen with alkaline medication. After five months of this therapy, his weakness, abdominal pain, and flatulence persisted, but he gained five pounds in weight. Gastroscopic examination on February 9, 1940, revealed some improvement, but the persistence of definite atrophy manifested by the continued presence of the large blood vessels and the markedly pale mucosa demanded the institution of more energetic therapy.

\*From the Medical and Gastro-Intestinal Clinics of the Indianapolis City Hospital and the Department of Internal Medicine of the Indiana University School of Medicine.

†Fellow in Gastro-Enterology at the Indianapolis City Hospital.

‡Furnished by Dr. Paul J. Fouts of the Lilly Laboratory for Clinical Research.

Submitted June 14, 1941.

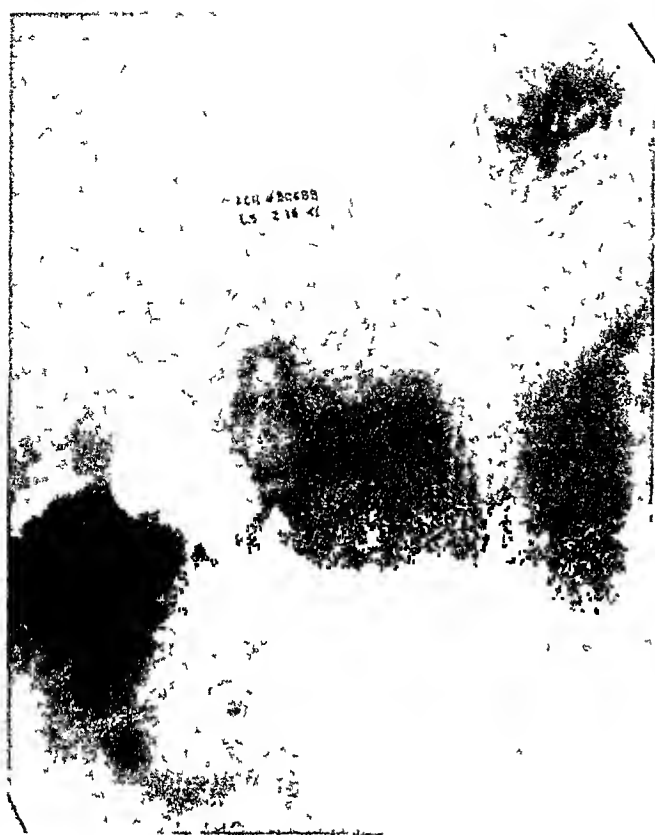


Fig. 2. Normal appearing stomach. No evidence of previous apparent greater curvature defect

Accordingly, twelve pulvules of Extralin per day were prescribed. After one month of this therapy, the patient stated that the epigastric burning and gnawing sensation had decreased, and he complained only of a feeling of fullness in the lower abdomen. In May, 1940, the patient volunteered the information that he was proud of the amount of work he was able to do.

Gastroscopic examination on December 4, 1940, after eleven months of Extralin therapy, revealed only a few small areas of mucosa slightly paler than normal. No blood vessels were visualized in the mucosa, indicating a marked reversion of the atrophic changes toward normal. The patient's only complaints at present are occasional lower abdominal distress and flatulence. A barium enema

in August, 1939, and May, 1941, has ruled out the presence of organic disease of the colon and terminal ileum. His weight has been stationary, although about fifteen pounds under his optimum. A complete blood count in May, 1941, revealed normal findings. A re-examination by X-ray in February, 1941, demonstrated a normal appearing stomach (Fig. 2).

## COMMENT

From the clinical history and X-ray findings, the tentative diagnosis was carcinoma of the stomach. The value of gastroscopy in distinguishing in this case between atrophic gastritis and carcinoma of the stomach was effectively demonstrated. The importance of repeated gastroscopic examinations is stressed as an objective check on the results of therapy. Since Konjetzny (6) has presented evidence that chronic atrophic gastritis may be a precursor of gastric carcinoma, the value of repeated gastroscopic studies to exclude the presence of early neoplastic changes too small to be recognized roentgenologically, is obvious. The beneficial effects of liver-stomach concentrate therapy on the clinical and gastroscopic picture in this patient confirm the observations of Schindler (7) and Schiff and Goodman (5) using similar preparations.

## CONCLUSIONS

A case history has been presented of a patient with gastroscopic evidence of chronic atrophic gastritis occurring as an isolated condition, responding with marked gastroscopic and symptomatic improvement to the oral administration of Extralin.

We are indebted to Doctor Mason Light for the gastroscopic examinations.

## REFERENCES

1. Chevallier, P. et Moutier, Fr.: Les gastrites atrophiques en aires: les gastrites atrophiques diffuses *Arch. d. mal. d. l'app. dig.*, 25:193, 1935
2. Schindler, R.: *Gastroscopy*. University of Chicago Press, Chicago, 1937
3. Schindler, R. and Murphy, H. M.: Symptomatology of Chronic Atrophic Gastritis *Am. J. Dig. Dis.*, 7:7, 1940.
4. Jones, C. M., Benedict, E. D. and Hampton, A. O.: Variations in the Gastric Mucosa in Pernicious Anemia. *Gastroscopic, Surgical, and Roentgenologic Observations*. *Am. J. M. Sci.*, 19:596, 1935.
5. Schiff, L. and Goodman, S.: Desiccated Hog's Stomach Extract (Ventriculin) in the Treatment of Atrophic Gastritis *Am. J. Dig. Dis.*, 7:14, 1940
6. Konjetzny, G. E.: *Der Magenkrebs*. Ferdinand Enke Stuttgart, 1938
7. Schindler, R.: Chronic Gastritis. *Rocky Mtn. M. J.*, 37:570, 1940.

# Halitosis, True and False

By

RUDOLPH DROSD, M.D.

and

BURRILL B. CROHN, M.D.

NEW YORK, NEW YORK

ONE who undertakes to treat cases of halitosis soon realizes that many people who come for treatment do not actually bear that condition. These patients usually suffer more mentally than do those who really have a bad breath. They are painfully "aware" of their bad breath and, as a result, have developed many mannerisms and subterfuges whereby

to disguise their breath. They are shy and retiring; they never speak directly to another person, but manage to keep the stream of their expiration directed away from the listener. Many become inveterate smokers and try to disguise their breath odors; others are constantly munching on scented mints or candy. These people finally become social outcasts of their own choosing. The "symptom" becomes as disabling as a major infirmity.

It is easy to demonstrate that persons with an of-

\*From the Medical Services of the Mount Sinai Hospital, New York City.

This study was aided by a grant from the Bristol Myers Co. Submitted January 20, 1942

fensive breath are rarely aware of it. This common observation becomes apparent to anyone who has the courage to ask the subject of a truly bad breath whether he is honestly conscious of it. The answer is frequently a rather shocked "no!" Or again, how often does the possessor of a reeking breath move about in public ignorant of this social handicap!

Simple experiments were performed to check this observation. Patients who were unaware of the type of medication were given garlic in capsules to swallow. The garlic could not contaminate the mouth when given in this manner. In one-half to one hour the breath of these patients reeked with garlic and was noticeable across an entire hospital ward. These patients noticed a faint garlic odor when they eructated shortly after ingesting the capsules, but thereafter were completely oblivious to the odor. No matter how long the odor lasted—12 to 36 hours—the carrier never recognized the odor on his own breath. When told by others that their breath was foul, these persons found it hard to believe. Those who did not eructate when the garlic was still in the stomach, were completely unaware that they had garlic halitosis. The same procedure was repeated with indol, skatol, and oil of peppermint with the same results. Neither the pleasant odor of peppermint, nor the stale odor of other drugs could be noticed by the patient. Indol and skatol, incidentally, gave odors similar to the constitutional types of halitosis.

The explanation of this negative consciousness is a simple matter. The sense of smell becomes adapted relatively quickly to a constant type of stimulus. Only sudden changes in the intensity of the stimulus can be noticed by the fatigued sense organ. Thus, during eructation, a strong odor rises momentarily from the stomach via the esophagus, and this can be detected even though the breath has been carrying the same odor in a milder degree for some time completely unknown to the patient. This eructation, however, gives the patient no inkling of the fact that his breath was malodorous before, and will continue to be so afterwards, for as soon as the odor due to the eructation is over, the patient will no longer recognize the milder but more constant odor from the breath.

Persons with true halitosis will seldom state that they notice the bad odor themselves; in fact, as soon as the patient states that he notices a bad odor on his own breath, the diagnosis of true halitosis can be seriously questioned. A person who has not, but thinks that he has, halitosis, is a much more unhappy individual than one who has actual halitosis. The subject of true halitosis is not unbearable to himself, but only to others. He is rendered unhappy at rare intervals, and only when told or reminded of his condition. The sufferer from false or subjective halitosis "notices" the bad breath constantly. He finds it hard to live with himself. It becomes almost impossible for him to maintain proper social relations.

Some years ago a patient reported himself for observation with the complaint of "bad breath." He was a shy reticent young man who shrank with evident reluctance when one attempted to sniff the odor of his mouth. He volunteered the information that he had been told on one occasion by his fiancée that his breath was "bad." Becoming obsessed with the idea, he had broken his engagement to marry, and retired from social contact. He avoided riding in

public vehicles lest fellow passengers show repugnance to his presence. He finally resigned his position as bank teller. On no occasion could one smell a disagreeable odor from his breath. But no amount of denial of its existence and no protestation of honesty of purpose succeeded in convincing him otherwise. With a sad shake of his head, and exhibiting openly his skepticism, he accepted some well-meant kindly advice, but with evident reservations. It was obvious that the patient was suffering with a "fixed idea," which was either an obsession as part of a compulsive neurosis, or a more serious symptom approaching a delusion. Some time later it was learned that he had committed suicide during a period of depression.

It is of interest to note that as a result of showing some occupation with the subject of halitosis, three patients have in the last few weeks appealed for help for a supposed condition of obnoxious mouth odor. Two of the three patients had perfectly normal sweet mouth odors and breath. One of the individuals had been told twenty-five years previously that his breath smelt badly; he had never to this day forgotten the incident and the resultant shock had left a lasting psychic impression. At this late date he too had an obsession that his breath was bad, and obviously no attempt at denial could convince him otherwise. His "bad breath" was finally conceded; with a diet and a mild intestinal purge, he was discharged happy in the idea that a cure would and could be effected.

#### VARIATIONS IN THE NORMAL BREATH

At various intervals during the day, anyone may have a moderately disagreeable breath. During sleep the reduced flow of saliva retards the normal cleansing action of the mouth and thus permits "morning mouth" which is fairly universal. Swallowing of saliva does not take place during profound sleep; apparently the secretion of saliva is markedly diminished. If the person is a mouth breather, the throat will become extremely dry and the voice will be hoarse on awakening. If saliva does continue to flow, it may drool from the corner of the mouth. But the absence of swallowing during sleep has an obvious effect on the waking breath. A person falling asleep with a candy in the mouth is likely to awaken shortly thereafter with his candy or lozenge undissolved in his cheek. The combination of dryness, the putrefaction of food remains in the dental interstices, and the cessation of the swallowing reflex combine to produce the disagreeable smell and taste upon awakening.

Volatile odoriferous foods eaten during the day appear readily on the breath. Most breaths have an unexplained stale odor just before meals when the individual is hungry. There is supposed to be a premenstrual disagreeable breath odor that lasts for several days. Certainly constant smokers have characteristically bad breaths. If during one of these normal odoriferous periods a person be told that his breath has an unpleasant odor, he may be so psychically impressed that a symptom of a neurosis originates.

#### BAD TASTE VERSUS BAD BREATH

A bad taste in the mouth is not to be confused with a true bad breath, though many persons may likely fall into such an error. The confusion between taste and odor is an understandable one. Few laymen understand the role that the sense of odor plays in the

sense of taste. Upon attempting to "taste" a volatile substance, the aroma will rise in the pharynx and nostrils and be smelt, so that smell is confused with taste. A young female patient was closely observed under normal conditions. At frequent intervals during the day, she was asked to describe the odor in her mouth, whether sweet or sour, neutral or unpleasant, etc. At the same periods a description of her breath odor was reported by an observer. Whenever an unpleasant breath odor was present, the patient was unaware of it or described her breath as "neutral." Often when the breath odor was pleasant or neutral, the patient would describe her breath as "slightly sour" or "stale." The only time the patient agreed with the observer was immediately after meals when the last item eaten could be detectable on the breath. These sensations reported by the patient were in all instances, actually tastes and not odors. The confusion between taste and odor accounts for the popularity of flavored substances in attempts to mask the odors on the breath. As long as the taste in the mouth is "sweet," these patients think that the breath odor is also sweet. This is not the case, however, for the taste from a sweet substance lasts much longer than does the odor therefrom. The breath in a patient with true halitosis may be highly disagreeable though the bearer deludes himself into thinking that the odor is being covered by a disguising medicament.

Neither the bad taste in the mouth, nor the coated tongue, nor halitosis for that matter have received adequate scientific attention, nor have they been reasonably and convincingly explained. A bad taste in the mouth may be associated with a coated tongue, but may not be such a concomitant or resultant; a coated tongue may be present and yet the subjective taste of the bearer be unaffected. Certainly halitosis may exist without either a conscious bad taste or a coated tongue.

Both coated tongue and bad breath are usually associated with some disturbance of gastric or intestinal function, resultant from over-eating in bulk or in quality, or from constipation. Just what is the mechanism by which the tongue is thickened and coated, and the breath made malodorous is not known. Neither pyloric delay nor intestinal hypomotility can be directly assigned as constant producing factors. But if they are the motivating forces, neither direct reverse peristalsis, nor gastric regurgitation, nor the reversed action of ciliated epithelium can be so impugned or proven.

There is no hesitation however in conceding the fact that occasional cases of halitosis are associated with a continuously coated and furry tongue. Recently we had occasion to hospitalize for observation a man who complained of "halitosis." His informant was his fond wife who consciously made him aware of the occasions upon which his breath was bad. During several days of observation it was noted that his

breath was obnoxious when his tongue was coated. A high fat, rich diet produced coated tongue and bad breath. On scraping and brushing the tongue much of the so-called halitosis disappeared; on reducing the diet and encouraging mild saline laxatives, his breath became normal.

Several factors may thus combine to produce halitosis or to be confused with it:

*Bad taste* alone is a subjective sensation, usually founded on an intestinal or gastric disturbance; it is not in itself related to, or productive of, bad breath odor.

*Coated tongue* is only occasionally the sole cause of halitosis, and probably only when a chronic disorder of intestinal indigestion or of fat metabolism and absorption exists.

*True halitosis* exists most often independent of taste or tongue changes; it is unknown to the patient. Its existence is consonant with a perfectly clean smooth glossal surface. The true or essential halitosis depends probably on some fault in fat digestion and its intestinal absorption and splitting; or, perhaps in some fault in the hepatic reassembly of fatty acid radicals and soaps with newer human equivalents of sterols and fats. In the course of this disturbance, intestinal or hepatic, volatile substances are absorbed into the circulatory medium and are excreted by the lungs on the expired air, tainting the breath with a malodor (1).

#### SPURIOUS HALITOSIS

A real problem concerns those who with an "idée fixe" are possessed with the obsession that they are sufferers of a real halitosis when none whatever exists. The underlying nature of the psychic disturbance is often difficult to establish. Whether it is an obsession as part of a compulsion neurosis, or whether it represents a more serious "fixed idea" resembling a delusion, must be determined by psychiatric investigation. Certainly it is the role of the psychiatrist, and not that of the internist, to determine the underlying psychic disturbances. The great difficulty is that of convincing a patient who hesitatingly and with tremendous reserve complains of halitosis, that what he really needs is psychiatric treatment.

To reassure such an individual with the reiterated statement that actually he has no bad breath, is completely ineffective and creates suspicion and resentment in the patient.

The time and patience and expense and perseverance necessary for adequate psychotherapy seems to a skeptical patient a far cry from his original complaint of halitosis. And yet without psychic relief the ultimate fate of sufferers of spurious halitosis is liable to be a most unhappy one, if it does not itself lead to a more tragic finale.

#### REFERENCE

1. Crohn, B. B. and Drosd, R.: *J. A. M. A.*

# The Effect of Acute Alcoholic Intoxication on Hepatic Function\*

By

J. M. BEAZELL, Ph.D., M.D.,\*\* A. L. BERMAN M.B., Ph.D.,† V. H. HOUGH, B.A.‡

and

A. C. IVY, Ph.D., M.D.§

CHICAGO, ILLINOIS

IT has been shown that under certain circumstances, acute alcoholic intoxication in the dog produces readily demonstrable liver damage from which the organ apparently recovers completely within two or three days. MacNider (1) found that alcohol administered so as to produce a state of semi-narcosis for a period of 12 hours resulted in an increase in the urinary excretion of phenolsulfonephthalein and a reduction in blood clearance of phenoltetrachlorophthalein. Histologic examination of liver tissue removed at biopsy revealed the typical changes which MacNider and Donnelly (2) had found to occur in certain dogs chronically intoxicated for periods ranging from 6 months to 2.5 years. The liver was characterized by peribular edema and cloudy swelling without necrosis. By the end of three days of abstinence from alcohol the dye elimination tests and the histology of the liver had returned essentially to normal. In a second series of animals maintained in a state of semi-narcosis for 24 hours the hepatic abnormalities were more marked and the period of recovery more prolonged.

Berman, Snapp and Ivy (3) found that 40 cc. of absolute alcohol, fed in 20 cc. doses with the meals to chronic biliary fistula dogs caused a marked reduction in cholic acid output, which these investigators consider a sensitive indicator of liver function. The volume output was not significantly depressed, but in all ten experiments the bile became murky, odoriferous, and resembled bile that is obtained in the presence of partial obstruction or acute hepatitis. The pigment and cholesterol outputs were not affected significantly. It is possible that the reduced cholic acid output was due to diminished protein catabolism resulting from a protein-sparing effect of the alcohol.

Hurst (4) used the fructose (levulose) tolerance test to evaluate hepatic function in 5 healthy young men before, and the morning after a "night out." As measured by this test, alcoholic intoxication resulted in an impairment of hepatic function. This study was accepted by Hurst as confirmation of his impression that hepatic dysfunction played an important part in producing the symptoms of a "hang-over."

MacNider's observations show that in the dog, acute liver damage will result from the administration of a quantity of alcohol sufficient to produce coma, and those of Hurst indicate that comparable changes occur in man in the presence of a more moderate degree of intoxication. Confirmation of Hurst's study would offer a partial solution to two problems. First, hepatic

dysfunction would account for some of the symptoms of the "hang-over." Second, the relationship between alcohol and portal cirrhosis would be further illuminated, i.e., if a single episode of alcoholic intoxication will produce acute liver damage, such insults frequently repeated might be expected to predispose to chronic fibrotic changes. In view of the importance of the question, the influence on hepatic function of a single episode of alcoholic intoxication has been investigated by means of multiple function tests.

## METHODS

Ten healthy young adult males who were accustomed to the occasional use of alcohol were used as subjects for the experiment. They were studied on two occasions separated by one week. The procedure in detail was as follows:

After eating their customary dinner at 6:00 p.m. the subjects were assembled at 8:00 p.m. and were given 6 cc. per kilo of a good grade of bonded bourbon whiskey with instructions to consume as much as possible over a period of 4 hours. According to their individual preference, the whiskey was either consumed undiluted or diluted with charged water or ginger ale. Thirty minutes after ingesting their last drink a blood sample for the determination of alcohol was obtained. It was at about this time that the subjects appeared to be maximally intoxicated, and this is the time, according to our previous experience, that maximal blood alcohol concentration usually occurs.

The subjects were kept under observation while they slept during the remainder of the night and at 10:00 a.m. the following morning liver function was evaluated by means of the following tests: Serum Van den Bergh, urine bilirubin, bromsulphthalein clearance, hippuric acid excretion, serum phosphatase, fasting blood sugar, and fructose or galactose tolerance. Not all of the tests were performed on each subject but as will be seen by examining Table I, each with the possible exception of fructose tolerance, was used in a sufficient number of cases to permit definite conclusions. In only one of the 7 attempts to use the fructose tolerance test was the test concluded. In the remaining 6 cases the subjects vomited before the termination of the test. Even so, the results leave little doubt as to the ability of the "post-alcoholic liver" to clear the blood of fructose. Vomiting also prevented completion of the hippuric acid and galactose tolerance tests in a number of instances (Table I).

To determine the effect of relatively larger doses of alcohol with consequent higher blood concentrations, 9 dogs were studied. The procedure was identical

\*From the Department of Physiology and Pharmacology, Northwestern University Medical School, Chicago, Ill.

†Assistant Professor of Physiology.

‡Fellow in Physiology.

§Fellow in Physiology.

§Nathan Smith Davis Professor of Physiology and Pharmacology.

Submitted January 15, 1942.



that used in the experiments on the human subjects except that the alcohol was administered after an 18 hour fast and only bromsulphthalein clearance, serum Van den Bergh, serum phosphatase, and galactose tolerance were used to evaluate hepatic function. Three cubic centimeters per kilo of 95 per cent alcohol in a 20 per cent solution was administered by stomach tube in three equal doses one hour apart.

In the hippuric acid test a 5 gm. dose of sodium benzoate was administered orally and the hippuric acid content of the urine collected during the subsequent 4 hours was determined. In the bromsulphthalein test 2 mgs. per kilo was administered to the human subjects and 5 mgs. per kilo to the dogs. The quantity of dye remaining in the blood at the end of 30 minutes was determined. Galactose tolerance was determined with a dose of 40 gms. for the humans and 20 gms. for the dogs. The galactose content of the urine collected during the subsequent 4 hours was determined. Urine was collected by means of catheterization in the case of the dogs. Serum phosphatase was determined by the method of Bodansky (5), the blood alcohol by the method of Friedemann and Klaas (6), and blood sugar by the Shaffer-Somogyi method (7).

### RESULTS

In the first series of experiments, marked intoxication was induced in all of the human subjects. They uniformly went through the cycle which is characteristic of alcoholic intoxication. Starting with an exaggerated sense of well being and excessive joviality, they progressed through moderate to severe motor incoordination, mental sluggishness and depression, and ended by being nauseated and vomiting. Eight had severe "hang-overs" which resulted in their

spending most of the day in bed. In the case of the other two, the "hang-over" was less incapacitating, but nevertheless distressing.

The correlation between the degree of intoxication, as judged by signs and symptoms, and the blood alcohol concentration was poor. Subject C. S., with a concentration of 171 mg. per 100 cc., was stuporous, markedly ataxic, and almost completely lacking in judgment at the time the blood sample was taken. On the other hand, subject D. Y., with a concentration of 201 mg. per 100 cc., retained fair control of his mental faculties and was only moderately ataxic. The former of these two subjects had consumed an intoxicating quantity of alcohol on only a few other occasions. It should not be concluded from this that the determination of blood alcohol concentration does not offer an objective measurement of intoxication. In all cases when the concentration exceeded 150 mg. per 100 cc. the subjects were "intoxicated" according to any definition of the term.

In the second series of experiments, three of the subjects were prevented by early nausea and vomiting from consuming sufficient whiskey to yield clear cut inebriation. The remaining subjects went through the same cycle of events as in the first test with the same results on the following day.

The results of the hepatic function tests in these experiments are summarized in Table I. Although 4 of the subjects had slightly elevated Van den Berghs, similar values were obtained on control samples of blood obtained 2 weeks after the last alcohol test. None of the other tests offered any evidence of disturbed liver function.

The results of the experiments on the dogs are summarized in Table II. Four of the 9 animals re-

TABLE I  
*The influence of acute alcoholic intoxication on hepatic function (human)*

| Subject | Wt. (Kilo) | First Period           |                        |                              |                    |                               |                     |                       |             |               |               | Second Period          |                        |                              |                    |                               |                     |                |             |               |               |
|---------|------------|------------------------|------------------------|------------------------------|--------------------|-------------------------------|---------------------|-----------------------|-------------|---------------|---------------|------------------------|------------------------|------------------------------|--------------------|-------------------------------|---------------------|----------------|-------------|---------------|---------------|
|         |            | Bourbon Consumed (cc.) | Alcohol Per Kilo (cc.) | Blood Alcohol (Mg. Per Cent) | Bromsul. Retention | Hippuric Acid Excretion (Gm.) | G-lactose Excretion | Blood Sugar†          | Phosphatase | Van den Bergh | Bilirubinurea | Bourbon Consumed (cc.) | Alcohol Per Kilo (cc.) | Blood Alcohol (Mg. Per Cent) | Bromsul. Retention | Hippuric Acid Excretion (Gm.) | Galactose Excretion | Blood Sugar†   | Phosphatase | Van den Bergh | Bilirubinurea |
| J.W.    | 80         | 360                    | 2.25                   | 163                          | 0                  | 2.15                          | 2.62                | —                     | 1.5         | —0.2          | 0             | 360                    | 2.25                   | 128                          | 0                  | 2.41                          | 0.77                | —              | 2.0         | —0.2          | 0             |
| H.A.    | 64         | 267                    | 2.08                   | 137                          | 0                  | 2.59                          | 0.56                | —                     | 2.3         | —0.2          | 0             | 237                    | 1.81                   | 26                           | 0                  | 2.21                          | 0.79                | —              | 2.0         | —0.2          | 0             |
| B.S.    | 90         | 508                    | 2.82                   | 168                          | 0                  | 2.55                          | 0.58                | —                     | 2.3         | —0.2          | 0             | 408                    | 2.27                   | 137                          | 0                  | 2.40                          | 0.39                | —              | 2.4         | —0.2          | 0             |
| D.Y.    | 70         | 350                    | 2.50                   | 201                          | 0                  | *                             | *                   | —                     | 2.1         | —0.2          | 0             | 305                    | 2.18                   | 146                          | 0                  | *                             | *                   | —              | 2.5         | —0.2          | 0             |
| C.S.    | 70         | 348                    | 2.48                   | 171                          | 0                  | *                             | *                   | —                     | 1.8         | —0.2          | 0             | 283                    | 2.03                   | 63                           | 0                  | 2.30                          | 0.63                | —              | 1.9         | —0.2          | 0             |
| W.      | 95         | 395                    | 2.08                   | 154                          | 0                  | *                             | *                   | —                     | 2.2         | —0.2          | 0             | 395                    | 2.03                   | 171                          | 0                  | *                             | *                   | —              | 2.7         | —0.2          | 0             |
| D.S.    | 70         | 395                    | 2.82                   | 188                          | 0                  | 1.93                          | —                   | 66*<br>63<br>65<br>45 | 2.8         | 0.5           | 0             | 260                    | 1.86                   | 43                           | 0                  | *                             | —                   | 67<br>70*      | 2.9         | 0.6           | 0             |
| A.S.    | 77         | 338                    | 2.19                   | 162                          | 0                  | *                             | —                   | 63<br>65<br>45        | 1.5         | 0.7           | 0             | —                      | —                      | —                            | —                  | —                             | —                   | —              | —           | —             | —             |
| W.M.    | 65         | 395                    | 3.0                    | 162                          | 0                  | *                             | —                   | 77<br>63<br>45        | 2.3         | 0.9           | 0             | 275                    | 2.08                   | 164                          | 0                  | *                             | —                   | 60<br>65*      | 2.5         | 0.5           | 0             |
| H.C.    | 70         | 370                    | 2.66                   | 162                          | 0                  | *                             | —                   | 80<br>63<br>45        | 2.8         | 1.0           | 0             | 380                    | 2.72                   | 137                          | 0                  | *                             | —                   | 95<br>63<br>45 | 3.5         | 1.15          | 0             |

\*Indicates that test was unsuccessful because subjects vomited sugar and sodium benzoate.  
†In descending order, values represent fasting and 1 hour and 2 hour samples after fructose.



tained dye and when the experiment was repeated on these 4 two weeks later, they again retained dye although they cleared the dye in the control experiment which was conducted during the interval between the two alcohol tests. This, coupled with the fact that in tests conducted on 35 normal animals we encountered no case of dye retention, appears to establish the significance of the observation. The cycle through which the dogs passed after administration of the alcohol was essentially the same as that noted in the human subjects.

### DISCUSSION

Acute alcoholic intoxication had no demonstrable ill effect on hepatic function according to the results obtained with the tests used, in any of the human subjects. This cannot be accepted as final proof that the liver was entirely unharmed. Since all of the subjects had "hang-overs," it appears safe to conclude that liver damage as detectible by the ordinary tests of liver function now available, plays no part in the production of this symptom complex. It seems unlikely, according to existing knowledge, that symptoms could be produced by a liver capable of normal benzoic acid conjugation, galactose and fructose conversion, and bromsulphthalein and bilirubin excretion.

The difference between man and dog with respect to bromsulphthalein clearance after alcohol appears to be due to a species difference in sensitivity to the hepato-toxic effect of alcohol. It cannot be attributed to a difference in the degree of intoxication since in 5 instances dye was retained when the blood alcohol concentration of the dogs fell into the same range as that observed in the humans. However, since the dogs, in contrast to the humans, were given the alcohol on an empty stomach, the resultant more rapid absorption may have yielded a higher alcohol concentration in the portal blood with a consequent greater immediate insult to the liver. It is possible also, though not likely, that previous use of alcohol had made the livers of the human subjects more resistant to its toxic effects. The results suggest that observations on the dog cannot be used without qualification to predict

the effect of alcohol on the liver in man. It cannot be said, of course, that a degree of intoxication comparable to that produced by MacNider (1) in the dog, would not produce liver dysfunction in man. Further, if it had been possible to determine the cholate content of the bile, acute liver damage may have been demonstrated by a depression of the cholic acid output as was found in biliary fistula animals intoxicated with alcohol (3).

The discrepancy between our observations and those of Hurst is difficult to explain, since our tests included the one he used. It is unlikely that Hurst's subjects were studied after a more advanced stage of intoxication, although this point cannot be evaluated since he did not determine blood alcohol concentration. It is implied that his subjects were studied after a night of "celebrating." Our subjects reached, and in most cases surpassed, the degree of intoxication one would expect to encounter in a group of "celebrants." Our subjects, with two exceptions, would have been incapable of making their way home.

Whether profound drunkenness in man (blood alcohol concentrations of 300 to 500 mg. per cent) results in liver dysfunction, detectible by existing tests, remains unanswered. As was suggested above, it appears probable that such advanced intoxication would result in demonstrable liver damage. Our results establish, however, that as measured by the tests employed in this study, the stage of intoxication reached by our subjects is without ill effect on the liver.

### SUMMARY AND CONCLUSIONS

Ten human subjects and 9 dogs were studied to determine the effect of acute alcoholic intoxication on hepatic function. On two occasions the human subjects consumed from 2 to 3 cc. of alcohol per kilo in the form of bourbon whiskey over a period of from 2½ to 4 hours. This resulted in blood alcohol concentrations ranging up to 205 mg. per cent. The following morning (10 hours later) the following tests were employed to evaluate hepatic function: Serum Van den Bergh, serum phosphatase, hippuric acid excretion, brom-

TABLE II  
*The influence of acute alcoholic intoxication on hepatic function (dog)*

| Dog No. | Wt. (Kilo) | Alcohol Per Kilo (cc.) | 1st Alcohol Experiment       |               |                          |                          | Control     |               |               |                    | 2nd Alcohol Experiment |               |               |               |                    |             |
|---------|------------|------------------------|------------------------------|---------------|--------------------------|--------------------------|-------------|---------------|---------------|--------------------|------------------------|---------------|---------------|---------------|--------------------|-------------|
|         |            |                        | Blood Alcohol (Mg. Per Cent) | Van den Bergh | Dye Retention (Per Cent) | Galactose Excreted (Gm.) | Phosphatase | Van den Bergh | Dye Retention | Galactose Excreted | Phosphatase            | Blood Alcohol | Van den Bergh | Dye Retention | Galactose Excreted | Phosphatase |
| 1       | 12.4       | 3                      | 206                          | 0             | 5                        | 6.9                      | —           | 0             | 0             | 7.2                | —                      | 205           | 0             | 5             | 8.2                | —           |
| 2       | 9.8        | 3                      | 184                          | 0             | 5                        | 5.1                      | —           | 0             | 0             | 5.5                | —                      | 154           | 0             | 10            | 4.3                | —           |
| 3       | 8.2        | 3                      | 193                          | 0             | 0                        | 5.7                      | —           | 0             | 0             | 7.8                | —                      | 176           | 0             | 0             | 19.3               | —           |
| 4       | 11.1       | 3                      | 235                          | 0             | 10                       | 5.2                      | 3.1         | —             | 0             | 4.6                | 5.4                    | 192           | —             | 15            | —                  | 5.6         |
| 5       | 8.4        | 3                      | 205                          | 0             | 5                        | —                        | 4.9         | —             | 0             | 5.2                | 4.4                    | 145           | —             | 10            | —                  | 5.4         |
| 6       | 5.9        | 3                      | 225                          | 0             | 0                        | 5.6                      | 1.3         | —             | —             | 7.1                | 3.4                    | —             | —             | —             | —                  | —           |
| 7       | 8.6        | 3                      | 274                          | 0             | 0                        | 6.6                      | 3.1         | —             | —             | 8.6                | 3.7                    | —             | —             | —             | —                  | —           |
| 8       | 8.6        | 3                      | 231                          | 0             | 0                        | 5.3                      | 2.8         | —             | —             | 3.57               | 4.8                    | —             | —             | —             | —                  | —           |
| 9       | 7.9        | 3                      | 141                          | 0             | 0                        | 5.5                      | 5.0         | —             | —             | 8.0                | 4.9                    | —             | —             | —             | —                  | —           |

snlphthalein clearance, urine bilirubin, fasting blood sugar, galactose tolerance, and fructose tolerance. In no case was there any evidence of a variation from the normal in these tests.

The dogs were given 3 cc. per kilo of 95 per cent alcohol in the form of a 20 per cent solution in three equal doses 1 hour apart. Ten hours later serum Van den Bergh, serum phosphatase, bromsulphthalein clearance, and galactose tolerance tests were conducted. Although no abnormality was demonstrated by the other tests, bromsulphthalein retention occurred in 4 of the 9 animals. In a second test on these 4 animals, dye retention again occurred although clearance was complete in a control experiment. These

observations suggest that the canine liver is more sensitive than the human liver to the hepato-toxic effects of alcohol.

These results establish that, as measured by the tests employed in this study, the stage of intoxication reached by our subjects is without ill effects on the human liver.

#### REFERENCES

- 1 MacNider, W. deB. : *J. Pharm. and Exp. Therap.*, 49:100, 1933
- 2 MacNider, W. deB. and Donnelly, G. L.: *Proc. Soc. Exp. Biol. and Med.*, 29:586, 1931.
- 3 Berman, A. L., Snapp, E. and Ivy, A. C.: *Quart. J. Studies on Ale.*, 1:645, 1941
- 4 Hurst, A.: *Brit. Med. J.*, 1:66, 1938.
- 5 Bodansky, A.: *J. Biol. Chem.*, 99:197, 1933
- 6 Friedemann, T. E. and Klans, R.: *J. Biol. Chem.*, 115:47, 1936
- 7 Shaffer, D. and Somogyi, M.: *J. Biol. Chem.*, 100:695, 1933

#### CONGRATULATIONS TO DR. MAX EINHORN ON HIS EIGHTIETH BIRTHDAY

*Editor's Note:* The Editors and Publisher of the "American Journal of Digestive Diseases" take pleasure in greeting Dr. Max Einhorn and congratulating him on his eightieth birthday. He was one of the founders of American gastro-enterology. The important facts about his life have been gathered in the following article by Dr. Hyman I. Goldstein, Camden, N. J.

**D**OCTOR EINHORN was born January 10, 1862, in Suchowol, a small town near Grodno (Russia, later Poland), the son of Abraham and Sara Einhorn. He attended Friedrich-Wilhelm Gymnasium; later, in 1879, he entered the government gymnasium in Riga. He was enrolled as a medical student in St. Wladimir University in Kiev. In 1881 he continued his studies in Friedrich-Wilhelm University in Berlin. In June, 1885, Doctor Einhorn arrived in New York and engaged in general practice in Harlem. In October, 1885, he became connected with the German Hospital (Lenox Hill Hospital) as house physician in the division of internal medicine, and physician in the German dispensary.

Doctor Einhorn was married to Flora Strauss of New York on March 30, 1892. It was in 1887, fifty-five years ago, when he began to specialize in gastrointestinal diseases. In March, 1888, he visited the clinic of Carl Anton Ewald in Berlin and worked with him for four months. He returned to New York in August, 1888, when he became assistant to Dr. J. Rudisch (1847-1926).

In 1889, Dr. Einhorn became Instructor in Internal Medicine of the New York Postgraduate Medical School and later became Associate Professor and Professor of Medicine. In 1922 he was made Professor Emeritus and consulting physician of the New York Postgraduate Medical School.

Fielding H. Garrison in his "History of Medicine" said of Einhorn he "has invented many ingenious devices and instruments, such as gastrodigraphy (1887), stomach-buckets (1890), duodenal-buckets (1908), and is the author of well-known treatises on diseases of the stomach (1896), of the intestines (1900) and dietetics (1905)." On page 736 Garrison states, "Duodenal intubation with the small tube is associated with the name of Einhorn."

In Professor Louis Ruyter Grote's "Die Medizin der Gegenwart in Selbstdarstellungen," volume 8, pages 1 to 24 (1929) there appears an autobiography by Max

Einhorn, including his bibliography of 176 publications to 1927. Dr. Einhorn now has to his credit more than 300 scientific contributions to medical literature, beginning with his Inaugural Dissertation, "Ueber das Verhalten der Lymphocyten zu den weissen Blutkörperchen." He is a Director of the "Archiv für Verdauungskrankheiten (since 1905) and is associate Editor of the "Medizinische Monatschrift."

In this brief sketch, mention should be made of his books on "Diseases of the stomach," "Diseases of the



MAX EINHORN (in 1929)

intestines," "Lectures on Dietetics," and "The Duodenal tube." Doctor Einhorn early used a metallic dilator for cardiospasm and his own modification of the esophagoscope, the powder blower and sprayer for direct treatment of the interior of the stomach.

He is an honorary member of the Gastro-Enterological Society of Japan, the National Gastro-Enterological Association, the American Gastro-Enterological Association, the Gastro-Enterological Society of Mexico, the German Society for Digestive Diseases,

Corresponding Member of the Medical Society of Munich and of Paris, and is an honorary Fellow of the Internal College of Surgeons.

## Ueber das Verhalten der Lymphocyten zu den weissen Blutkörperchen.

### INAUGURAL-DISSERTATION

REDAKTION DER DOCTOREN

IN 1902

## MEDICIN UND CHIRURGIE

VERLAGT VON

MEDICINISCHEN FACULTÄT

IN

• FRIEDRICH-WILHELMS-UNIVERSITÄT ZU BERLIN

AM 21. März 1901

MAX EINHORN

am Graduiert in Medizin

OPPOSITEN:

Herr Dr. A. Göttsch

Herr Dr. phil. et cand. med. I. Nathan

Herr cand. med. V. Braucamp

BERLIN

(Einhorn's First Publication)

MAX EINHORN

1. Achylia Gastrica simulans hyperchlorhydria. In Festschrift in honor of Abraham Jacobi, pp. 41-45, 1900.
2. Die Behandlung des Magenkrebses in America. In Internat. Beiträge zur ... Ernährungsgeschichte ... Vol. I, 1910.
3. Dimethylamidoarobenzol, or Teopfer's Test for Free Hydrochloric Acid. N. Y. Med. J., 63, 1896; N. Y. Appleton, 2 pp., 1896.
4. Diseases of the Intestines. A text-book for practitioners and students of medicine 391 pp., N. Y., Wood, 1900.

5. Second Edition, 397 pp., N. Y., Wood, 1904.
6. Diseases of the Stomach. In Stedman, T. L., Editor. Text-book of Century Practice, Vol. 8, pp. 115-367, 1905.
7. Diseases of the Stomach: a text-book for practitioners and students, 475 pp., N. Y., Wood, 1897.
8. 2nd Ed., 486 pp., N. Y., Wood, 1897.
9. 3rd Ed., 534 pp., N. Y., Wood, 1903.
10. 4th Ed., 559 pp., N. Y., Wood, 1906.
11. 5th Ed., 531 pp., N. Y., Wood, 1911.
12. 6th Ed., 569 pp., N. Y., Wood & Co., 1917.
13. 7th Ed., 581 pp., N. Y., Wood & Co., 1921.
14. The Duodenal Tube and its Possibilities, 122 pp., 1917, Saunders, Philadelphia.
15. 2nd Ed., 206 pp., F. A. Davis Co., Phila., 1925.
16. Enteroptosis. Med. News, 60, 1896; N. Y., 8 pp., 1896.
17. Further Report on Achylia Gastrica 21 pp. Trow, N. Y., 1897; Med. Rec., 48, 1895.
18. Historische Skizze der Entwicklung der Fermentation zur Bedeutung der Funktionen des Verdauungstraktes. In Internat. Beiträge ... Ernährungsgeschichte ... Vol. 4, pp. 19-42, 1918.
19. Lectures on Dietetics, 156 pp., N. Y., Hoeber, 1914.
20. Lectures on Dietetics, 2nd Ed., 244 pp., W. B. Saunders Co., Phila., 1922.
21. Practical Problems of Diet and Nutrition 61 pp., N. Y., W. B. Saunders, 1907.
22. Report of a case of Narrowing and Constant Patency of the Pylorus. In N. Y. Post-Graduate Medical School and Hospital Contributions, pp. 126-129, 1903.
23. Simultaneous Gastro-Duodenal Aspirator. In Contributions Dedicated to Sir William Osler, Vol. 1, pp. 478-479, 1910.
24. Weitere Erfahrungen mit der Fadenprobe zur Erkennung von Geschwüren des oberen Verdauungstraktes ... In Festschrift ... d. Deutsch. Hosp., pp. 56-60, 1909.
25. With J. Rosenbloom—Eine Studie über den Stickstoffmetabolismus in drei Fällen von Duodenalernährung. In Internat. Beiträge zur ... Ernährungsgeschichte ... Vol. 3, pp. 59, 1912.
26. Importance of the Colloidal Nitrogen of the Urine in the Diagnosis of Cancer. In Columbia Univ., N. Y., Studies in cancer and allied subjects, Vol. 3, pp. 200-205, 1911; Am. J. Cancer, 1911.
27. On Functional Disorders of the Stomach Accompanied with Hypersecretion. (1) Hyperchlorhydria. (2) Gastro-succorhoea continua periodica. (3) Gastro-succorhoea continua chronica 24 pp., N. Y., 1895; Med. Rec., Vol. 48, 1895.
28. State of the Gastric Mucosa in Secretory Disorders of the Stomach 11 pp., Publ. Pr. Co., 1896; Med. Rec., Vol. 49, 1896.
29. Treatment of Habitual Constipation. 7 pp., N. Y., 1895, Post-Graduate, Vol. 11, 1896.
30. Die Prophylaxie in der inneren Medizin. In Nabrig, A. and Janlau, L., Editors, Handb. d. Prophylaxe, part 16, pp. 45-56, 1901.
31. Index Catalogue of The Library of the Surgeon General's Office U. S. Army, Second Series, Vol. IV, p. 784, Washington, D. C., 1899.
32. "Ein Fall von Wanderleber." Med. Monatsschrift (N. Y. C.), 1:351-353 (Jan.-Dec., 1891). (Ectopia hepatis oder Hepa migrans).
33. Die Rumination beim Menschen. Med. Monatsschrift (N. Y. C.) 2:228-230, Jan.-Dec., 1890.
34. Probemittagbrot oder Probefrühstück. Aus der städtischen Krankenanstalt zu Berlin, 9 pp.; Berliner klin. Wochenschr., 27, 1890.

Hyman I. Goldstein, Camden, N. J., M.D.

Dr. Goldstein was president of the New Jersey Gastro-Enterology Society (1941) and Chairman (1910) of the Section on Gastro-Enterology, State Medical Society of New Jersey.

## Abstracts of Current Literature

FRANKLIN HOLLANDER, Associate Editor in Charge of Abstracts, New York, N. Y.

ALBERT CORNELL, New York, N. Y.  
MAURICE FELDMAN, Baltimore, Md.  
CHARLES A. FLOOD, New York, N. Y.  
M. H. FRIEDMAN, Philadelphia, Pa.  
J. DUFFY HANCOCK, Louisville, Ky.  
THOMAS A. JOHNSON, Philadelphia, Pa.  
ALLEN A. JONES, Buffalo, N. Y.  
N. W. JONES, Portland, Ore.  
HENRY H. LERNER, Boston, Mass.  
PHILIP LEVITSKY, Montreal, Can.

JESSIE LOVE, Louisville, Ky.  
FRANZ J. LUST, New York, N. Y.  
IRA A. MANVILLE, Portland, Ore.  
ARTHUR E. MEYER, Brooklyn, N. Y.  
FRANCIS MURPHY, Milwaukee, Wis.  
H. NECHES, Chicago, Ill.  
FRANK NEUWELT, Gary, Indiana  
SAM OVERSTREET, Louisville, Ky.  
J. F. PESSEL, Trenton, N. J.  
DAVID J. SANDWEISS, Detroit, Mich.

RUDOLPH SCHINDLER, Chicago, Ill.  
MICHAEL SHUTKIN, Milwaukee, Wis.  
VIRGIL E. SIMPSON, Louisville, Ky.  
H. J. SIMS, Denver, Colo.  
HENRY TUMEN, Philadelphia, Pa.  
ROBERT TURELL, New York, N. Y.  
EDGAR WAYBURN, San Francisco, Cal.  
JOHN WILLARD, Philadelphia, Pa.  
C. WILMER WIRTH, Philadelphia, Pa.

### CLINICAL MEDICINE STOMACH

McCLURE, SWFETSIK AND JANKELSON: Chronic Gastritis: A Gastroscopic and Clinical Study. New Eng. J. Med., 275:259, Aug., 1911.

In a study of 611 cases the authors note the presence of chronic gastritis in 44%. Although mixed types were present in 47% of the cases the authors were able to differentiate between the hypertrophic (56%) atrophic (90%) and superficial (25%) gastritis.

75 patients were studied for the purpose of evaluating the symptomatology. The symptoms associated with hypertrophic and atrophic gastritis were the same except for fatigability which characterized the primary atrophic gastritis. In a small number of ulcer patients the

symptomatology was modified in the presence of chronic gastritis.—H. H. Lerner.

GARLOCK, JOHN H.: The Problem of Carcinoma of the Cardiac End of the Stomach. S. G. O., 73:244, Aug., 1911.

The author has operated upon twenty-five patients with carcinoma of the cardia of the stomach and in nine of these an operative procedure in addition to exploratory was able to be carried out. Only four patients died operatively, and they were among this latter group. The results suggest that a patient with an operable carcinoma of the cardia can be offered a sixty per cent chance of surviving an attempt at radical removal.—C. Wilmer Wirth.

## Prognosis of Regional Enteritis

By

PHILIP W. BROWN, M.D.†

and

CHARLES J. DONALD, JR., M.D.‡

ROCHESTER, MINNESOTA

IT is appropriate to present to this society the information that we have gained from the follow-up study of patients suffering from this disease. The stimulation and organization of our work in this disease were derived from the original work of Crohn, Ginzburg and Oppenheimer (1), reported in 1932 before the Section on Gastro-Enterology and Proctology of the American Medical Association. In the following year Bergen, Weber and one of us (Brown (2)) presented a report and suggested the more comprehensive title of "regional enteritis" for the condition. It is interesting to see accounts such as that of Hurst (3), who in 1939 described two cases in which patients who really had regional enteritis were operated on by Lord Moynihan fifteen and fourteen years previously with the diagnosis of "tuberculosis." Undoubtedly, in all hospitals there are tucked away many such instances under the diagnosis of "tuberculosis" or "granuloma," but not until Crohn and his associates had accumulated several such cases was it possible to approach the problem as an entity. The earliest record of a probable case that we have found is one reported by Morgagni (4) in about 1700. He described the findings at necropsy concerning a patient of Valsalva—a young man who had suffered from diarrhea and who on necropsy was found to have had an ulcerated process involving the terminal portion of the ileum, a process which extended into the colon. Excellent pathologic descriptions of what we would probably classify as "regional enteritis" were found by Sherrill and Hall (5) in their perusal of old records. They discovered that a case was reported in 1806 to the Royal College of Physicians and that in 1828 other cases were reported to the College.

### GENERAL CONSIDERATIONS

There is a question as to whether there is an increase in the incidence or in the recognition of this particular disease (Fig. 1). Although it is true that at the Mayo Clinic we have knowledge of only two such cases in 1922 and no others until 1929, we think it probable that there must be cases in that interval which were filed under obscure or indefinite diagnoses. As our scrutiny of unusual cases increased, it was noted that twenty-four instances of the condition were encountered prior to 1933. The recording of 114 cases at the Mayo Clinic in the past four years represents such a disproportionate increase in relationship to general clinic registration that it seems to indicate an increasing trend in the incidence of the disease and not merely more acute recognition of the condition itself.

Because we are concerned with the prognosis of

this disease, no detailed account of the clinical observations will be included herein other than a summary of the general pattern of material which constitutes our experience. Our data are based on the records of 178 patients. We deplore the fact that we have no knowledge of the etiology of the disease. The age and sex of the aforementioned patients are shown in Table I.

Of interest, but whether it is significant we cannot say, is the fact that 26 per cent of the patients were Jewish and 73 per cent were gentile. Furthermore, 70 per cent of the Jewish patients were less than thirty years old and only 38 per cent of the gentile patients were less than thirty years old. The group is too small to permit formation of conclusions, but results of the study would seem to indicate a greater vulnerability of the Jewish race to this disease.

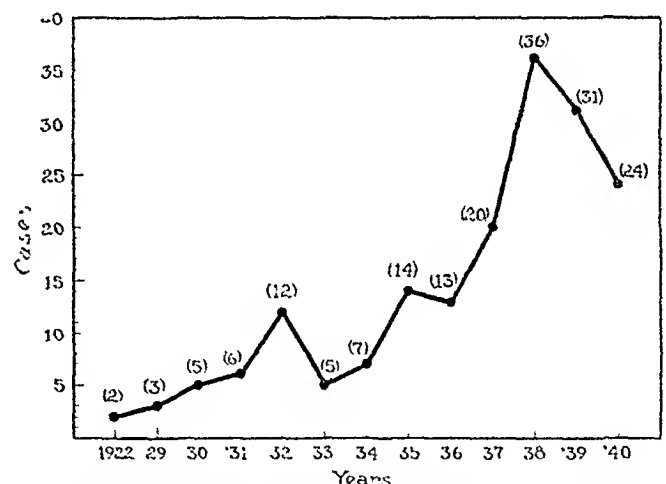


Fig. 1. Incidence of regional enteritis as recorded at the Mayo Clinic, 1922 to 1941.

The symptomatology conforms to previous observations as to abdominal pain, diarrhea, fever, anemia, development of fistula, loss of weight, nausea and vomiting, which occur most commonly and in the order named. In three instances, gross hemorrhage from the bowel had occurred.

Although the aforementioned symptoms and observations suggest the probability of regional enteritis, roentgenologic examination is the most important single contribution to a positive diagnosis. By means of the barium enema, evidence of disease was established in 124 instances and the barium meal identified seven additional instances not disclosed by the opaque enema. However, the roentgenologic examination is not infallible because the examiner may be unable to recognize the disease. Likewise, a roent-

\*Read before the meeting of the American Gastro-Enterological Association, Atlantic City, New Jersey, May 5 to 6, 1941.

†Division of Medicine, Mayo Clinic.

‡Fellow in Surgery, Mayo Foundation.

TABLE I

*Age and sex: 178 patients suffering from regional enteritis encountered at Mayo Clinic, 1922 to 1941*

| Sex    | Age, Years |          |          |          |          |          |             | Total |
|--------|------------|----------|----------|----------|----------|----------|-------------|-------|
|        | 0 to 10    | 10 to 20 | 20 to 30 | 30 to 40 | 40 to 50 | 50 to 60 | 60 and over |       |
| Male   | 1          | 10       | 27       | 29       | 13       | 4        | 2           | 67    |
| Female | 2          | 8        | 35       | 23       | 9        | 7        | 3           | 67    |
| Totals | 3          | 18       | 62       | 52       | 22       | 11       | 5           | 133   |

genologic report of a normal colon and normal terminal part of the ileum could not be expected to exclude an area of enteritis located more orad in the small bowel. Fortunately, in the large majority (92 per cent) of cases the disease is situated in the lower part of the ileum and often extends into the colon (Table II).

In Table II are included the forty-five instances in which fistulas occurred. Usually—probably invariably—external fistulas follow on the heels of antecedent surgical operation. Of greater interest, and certainly of greater concern to the surgeon, are the internal fistulas which are manifestations of the viciousness of the disease. From the diseased segment, the process may burrow into any adjacent loop of any piece of bowel or into the bladder.

### SURGICAL CONSIDERATIONS

This disease certainly has afforded the surgeon many a difficult experience. Of our group of 178 patients, eighty-two had been operated upon one or more times. In twelve instances resection of the bowel had been performed and in twelve others, a short circuit around the diseased portion of bowel had been established. Forty-seven patients had undergone appendectomy and for only fourteen was information available as to recognition of disease in the lower part of the ileum. In nine instances the abdomen had been closed after surgical exploration. Of course, a patient's report on findings at operation cannot be too fully accepted and in several instances such a report is all that we have.

Our knowledge of what has happened to these 178 patients is embraced in Table III and is summarized in Table IV. It is not possible to predict the eventual status of the twenty-nine patients (Table IV) whose condition we have listed as "fair." They are not invalids but we cannot consider them as "well." As

with patients who have peptic ulcer and chronic ulcerative colitis, we prefer to use the term "well" and not "cured."

On the basis of this particular study it may be added if the two-stage operative procedure is not preferable to the one-stage operation. The immediate mortality rate is lower and the ultimate result seems better (Table IV) when the two-stage operation is used. The four patients who died post-operatively and the two who died later, among the forty-two who underwent the one-stage operation, were found to have acute to subacute enteritis at the time of operation. The same was true of the two patients who died after the two-stage operation. Both had an actively diseased bowel at the time of resection.

In analyzing the question of whether less favorable results, as well as definite recurrences, are more common among patients who had acute or subacute enteritis rather than the more chronic stage at the time of resection, there is no significant difference in results obtained for patients in each group. If the results called "fair" and the instances in which recurrence was definite are grouped together, it would seem that more patients are not well after one-stage resection than are not well after a two-stage procedure. However, such conclusions would be of no avail; too many intangible factors are involved.

As would be expected, the fate of those who require repeated resection of the bowel is not encouraging. Only fourteen of twenty-three patients so treated are known to survive, of whom we consider only four as "well" (the figure of fourteen does not include one patient concerning whom we have no follow-up data).

The additional complication of fistula complicates the surgical problem, and yet the results for patients in this group are far from being utterly discouraging. Among forty-three of forty-five such patients

TABLE II  
*Situation, regional enteritis and fistulas: 178 cases*

| Enteritis, Situation               | Cases | Type of Fistula Present, Instances |          |                       | Total (Fistulas) |
|------------------------------------|-------|------------------------------------|----------|-----------------------|------------------|
|                                    |       | Internal                           | External | Internal and External |                  |
| Jejunum                            | 5     | 0                                  | 0        | 0                     | 0                |
| Ileum, upper part or most of ileum | 1     | 0                                  | 1        | 0                     | 1                |
| Ileum, lower                       | 29    | 4                                  | 16       | 3                     | 23               |
| Ileum and into colon               | 67    | 4                                  | 14       | 3                     | 21               |
| Totals                             | 178   | 8                                  | 31       | 6                     | 45               |

TABLE III  
*Status of patients, various years after treatment: 178 cases of regional enteritis*

| Procedure Employed  | Time After Operation or Examination, Years |      |      |        |      |      |        |      |      |        |      |      | Cases     |      |      | Totals |            |             |         |
|---------------------|--|------|------|--------|------|------|--------|------|------|--------|------|------|-----------|------|------|--------|------------|-------------|---------|
|                     | Under 1                                    |      |      | 1 to 3 |      |      | 3 to 5 |      |      | 5 to 7 |      |      | 8 or more |      |      |        |            |             |         |
|                     | Well                                       | Fair | Sick | Well   | Fair | Sick | Well   | Fair | Sick | Well   | Fair | Sick | Well      | Fair | Sick |        | P.O. Death | Death Later | No Data |
| One stage resection | 7  | 1    | 1    | 5      | 4    | 3    | 6      | 1    | 2    | 1      | 1    | 0    | 2         | 0    | 1    | 4      | 2          | 1           | 42      |
| Two stage resection | 8  | 2    | 1    | 20     | 6    | 1    | 5      | 3    | 0    | 3      | 0    | 0    | 4         | 0    | 1    | 1      | 1          | 0           | 56      |
| Reoperation         | 2  | 2    | 3    | 1      | 1    | 0    | 1      | 0    | 1    | 0      | 0    | 2    | 0         | 0    | 1    | 3      | 5          | 1           | 23      |
| Short circuit only  | 3  | 1    | 0    | 4      | 1    | 0    | 3      | 1    | 0    | 1      | 2    | 2    | 3         | 0    | 1    | 7      | 2          | 0           | 31      |
| Exploration only    | 0  | 1*   | 0    | 1†     | 0    | 1*   | 2†     | 1†   | 1*   | 2†     | 1†   | 0    | 2†        | 0    | 1*   | 1*     | 3*         | 1†          | 18      |
| No operation        | 0  | 0    | 3*   | 1      | 0    | 0    | 0      | 0    | 0    | 0      | 0    | 0    | 0         | 0    | 0    | 0      | 4‡         | 0           | 8       |
| Totals              | 20   | 7    | 8    | 32     | 12   | 5    | 17     | 6    | 4    | 7      | 4    | 4    | 11        | 0    | 5    | 16     | 17         | 3           | 178     |

\*Inoperable: Enteritis too extensive.

†Enteritis not severe enough for resection.

‡Two of the four patients who died, refused operation.

cerning whom there are data, twenty are apparently well; nineteen after resection and one after only "short-circuit." Fourteen are in fair to bad health, of whom eleven underwent resection, two underwent short-circuiting and one underwent drainage only. Nine are dead; four after resection, four after "short-circuit" and one after drainage. Nine deaths in the group of forty-five (20 per cent) constitute a much better mortality rate than one might expect. We do not minimize the added danger of fistulas, especially if internal fistulas exist, but the situation is by no means hopeless in competent surgical hands.

The group (thirty-one patients) for whom "short-circuit" was done requires study (Table IV). There was an immediate loss of seven patients in this group, all of whom were seriously ill. Four had active disease and three had extensive intestinal damage; of these three, one had multiple abdominal fistulas and one had several "skip" regions in the ileum. The two

patients who died later at home (Table IV) likewise had acute disease at the time of operation. Hence, of twenty-two survivors, fourteen were well at the time of this study, but only seven had lived for three or more years after operation (Table III).

The surgeon is constantly confronted with the problem of whether or not to continue to delay resection, after a preliminary "short-circuit," when the patient is in apparent good health. He is torn between knowledge of the ravages of the disease when it becomes acute and the encouragement offered by the patient's good condition. It is our opinion that in such circumstances resection should be undertaken, for it may be—and usually is—more serious to resect if the operation is delayed until exacerbation of the disease occurs.

To approach the problem from another aspect, we may point out that in our series of 178 patients there were twenty-three who had undergone a "short-

TABLE IV  
*Summary: Condition of patients at time of this report: 178 cases of regional enteritis*

| Treatment              | End Result for Patient |              |        |              |        |              |               |              |                |              |            |              | Totals<br>(Numbers) |
|------------------------|------------------------|--------------|--------|--------------|--------|--------------|---------------|--------------|----------------|--------------|------------|--------------|---------------------|
|                        | Well                   |              | Fair   |              | Sick   |              | P.O.<br>Death |              | Death<br>Later |              | No<br>Data |              |                     |
|                        | Number                 | Per<br>Cent* | Number | Per<br>Cent* | Number | Per<br>Cent* | Number        | Per<br>Cent* | Number         | Per<br>Cent* | Number     | Per<br>Cent* |                     |
| One stage<br>operation | 21                     | 50           | 7      | 17           | 7      | 17           | 4             | 9            | 2              | 5            | 1          | 2            | 42                  |
| Two stage<br>operation | 40                     | 71           | 11     | 20           | 3      | 5            | 1             | 2            | 1              | 2            | 0          | 0            | 56                  |
| Reoperation            | 4                      | 17           | 3      | 13           | 7      | 31           | 3             | 13           | 5              | 22           | 1          | 4            | 23                  |
| "Short-<br>circuit"    | 14                     | 45           | 5      | 16           | 3      | 10           | 7             | 23           | 2              | 6            | 0          | 0            | 31                  |
| Exploration<br>only†   | 7                      | 38           | 3      | 17           | 3      | 17           | 1             | 6            | 3              | 16           | 1          | 6            | 18                  |
| No operation           | 1                      | 13           | 0      | 0            | 3      | 37           | 0             | 0            | 4              | 50           | 0          | 0            | 8                   |
| Totals                 | 87                     | 49           | 29     | 16           | 26     | 14           | 16            | 9            | 17             | 10           | 3          | 2            | 178                 |

\*Percentages estimated on total original number in each group; not on number of survivors in each group.

†Eighteen patients in original group; condition in 8 at exploration was too extensive for operation; 3 of these are now in poor to serious health, 1 is in fair health and 4 are dead. Condition of remaining 10 in this group at exploration was early acute, not requiring resection; 7 of these are now well, 2 are in fair health; no data concerning 1. Total, 18.



circuiting" operation\* elsewhere before we saw them (these patients do not appear in tables of this paper or elsewhere in the text). It was found that these twenty-three patients had suffered from enteritis for from one to thirteen years after the disease had first been recognized to be present. Although we found that ten of these patients had begun to suffer from the disease within a year of the time they underwent resection at the Mayo Clinic, three had had the disease for eight years and one had had it for thirteen years.

It has been mentioned that thirty-one other patients underwent a "short-circuiting" operation at the Mayo Clinic (Table IV). Twenty-two of these patients survived the procedure. If the twenty-three patients mentioned in the preceding paragraph are added to the twenty-two patients in this paragraph, the result is forty-five patients for whom only a "short-circuiting" operation was first done. More than half of these forty-five patients (that is, the twenty-three who underwent "short-circuiting" operations elsewhere) had to undergo a second operation for enteritis, and only fourteen of the forty-five were considered to be well, without necessity for re-operation (Table IV), at the time of this report. Seven of these fourteen patients had not lived in good health for more than three years after operation at the time of this report (Table III). We agree with Crohn (6) that "short-circuiting" operations offer success in not more than 50 per cent of cases, and the percentage of success probably is nearer 25 than 50.

In the course of emergency surgical operation, when there is a pre-operative diagnosis of "probable acute appendicitis," there occurs from time to time the question of what to do at operation—or later—for the patient found to have acute regional enteritis. Ten such cases have come to our attention. As Table IV indicates, seven patients are well, three are not well and concerning one we have no data. We share the same anxiety as do others as to the ultimate result obtained for these patients, even though six were still well at the time of writing, three or more years after operation. We advise that the patient be kept under observation so that operation will not be delayed if complete resolution does not occur. Our experience coincides with that of Crohn (6), in that our necropsy records reveal no instance of healed chronic regional enteritis, although in some cases in which fulminating acute enteritis is present, resolution seems to occur.

### MEDICAL CONSIDERATIONS

In the light of our present lack of knowledge, surgery is the treatment of choice for regional enteritis. We do not know of any medical treatment that is of value in the sense of a "cure" of the disease.

Most informed physicians are more aware than ever before of the startling extent of submarginal nutrition that exists here and abroad. Before this society it is needless to justify any argument for an adequate intake of protein, minerals, fats and vitamins. Patients who have disease of the gastro-intestinal tract which has led to modification of a probably marginal diet, or patients who lose food by vomiting or diarrhea inevitably are in a state of some sort of nutritional de-

ficiency, and the deficiency usually is severe rather than mild.

Patients who have regional enteritis suffer from more than merely a lack of food, since when this disease is present actual interference with absorption of essential substances, especially of the Vitamin B group, seems to occur. In our series several patients, after resection, had to receive injections of liver extract regularly to maintain a fair degree of health. Bockus (7) likewise has commented on this problem. Such patients are among those classified as being in "fair" health, although they maintain themselves fairly well if regular and sufficient amounts of liver substance are provided. Liver extract must be administered parenterally to these patients. However, a much larger group of patients do not manifest such phenomena, and seem to be entirely normal, as has been noted by Jordan (8). Nevertheless, there are many who complain of fatigue, languor and general lack of endurance. In fact, some of them report that they had not realized that this mild exhaustion state was present until they had begun to take Vitamin B complex and had then discontinued it. We advise that all our patients supplement their food with Vitamin B complex. The size and cost of the dose are factors not to be disregarded, but it is the amount of Vitamin B products in the dose which is essentially the first consideration. We suggest a supplementary dose which will include not less than 3 mg. of thiamin, 1 mg. of riboflavin, 20 mg. of nicotinic acid, as well as declared values of pyridoxine and pantothenic acid. It has seemed to us that liquid preparations of B complex are preferable to those in dry form. If the product is kept cold, it is more palatable. However, we realize that cold or flavoring does not entirely dispel the rather unpleasant taste of yeast, liver or rice-bran preparations. A preparation of B complex for parenteral administration is being investigated and may offer more than liver extracts now in use for those patients who cannot absorb enough of the Vitamin B factor to produce normal maturation of erythrocytes and to maintain normal nutrition.

We regard anemia, failure to gain weight and strength, and diarrhea as ominous signs. They may indicate recurrence (or progression) of the disease. However, if roentgenologic studies disclose no evidence of abnormality, it may be judged that it is more that a nutritional difficulty is present than it is that recurrence has occurred—and hope that such an opinion is correct!

Persistent post-operative diarrhea is a rather common problem among patients who have undergone ileocolostomy. Approximately three-fourths of such patients in our series complained of this post-operative difficulty. Resection of a diseased segment of small intestine, with entero-anastomosis, usually is not followed by post-operative diarrhea. It would appear that either loss of the ileocecal normal junction or, more likely, loss of the liquid-absorbing portion of the right portion of the colon, is the reason for post-operative diarrhea. As previously noted, such diarrhea may indicate progression or recurrence of enteritis but also may be related only to disturbance of physiologic function. A low residue diet, with essential supplements and one to two teaspoonfuls daily of an inert absorbent material may suffice to relieve the

\*In some cases this "short-circuiting" operation had been done for conditions not recorded as enteritis, but in each case a diseased area had been found during the operation.

distress. Addition of extra sodium in the form of sodium chloride or citrate occasionally has been of benefit. Avoidance of ingestion of food or drink between meals has aided some patients. (Patients for whom this symptom, diarrhea, has been particularly troublesome have been classified in our series as being in "fair" health). Of psychologic value and of no great danger is the practice of permitting the patient to take an occasional teaspoonful of paregoric on "special occasions."

### CONCLUSIONS

1. Chronic regional enteritis is a serious disease which may originate at any point in the small intestine. In 92 per cent of our cases the disease originated in the terminal portion of the ileum.

2. The disease is characterized by remissions and exacerbations similar to those encountered among patients who have peptic ulcer and chronic ulcerative colitis.

3. The disease tends to progress, either orad or caudad, with increasing failure of absorption, even to the point of actual starvation of the patient because of failure to absorb food.

4. It is a disease which may affect persons of any

age but is more common among youths and young adult persons.

5. In the light of present knowledge—or lack of it—the treatment of choice is surgical removal of the diseased segment of bowel. Our study would suggest that the two-stage procedure is better than a one-stage operation.

6. The most important feature in post-operative care is maintenance of a high protein diet which is supplemented with components of the Vitamin B group.

### REFERENCES

1. Crohn, B. B., Ginzburg, Leon and Oppenheimer, G. D.: Regional Ileitis. *J. A. M. A.*, 99:1323-1329, Oct. 15, 1932.
2. Brown, P. W., Barges, J. A. and Weber, H. M.: Chronic Inflammatory Lesions of the Small Intestine; (Regional Enteritis). *Tr. Am. Gastro-Enterol. A.*, pp. 2-7, 1934.
3. Hurst, Arthur: Regional Ileitis (Crohn's Disease). *Guy's Hosp. Rep.*, 89:54-82, Jan., 1939.
4. Morgagni, J. B.: The Seats and Causes of Diseases Investigated by Anatomy. (Translated by Benjamin Alexander). London, A. Millar and T. Cadell, Vol. 2, p. 75, 1769.
5. Sherrill, J. G. and Hall, D. P.: Regional Ileitis. *Am. J. Surg.*, 48:669-674, June, 1940.
6. Crohn, B. B.: Regional Ileitis. *Am. J. Surg.*, 46:74-78, Oct., 1939.
7. Beckus, H. L., Johnson, T. A. and Lee, W. E.: An Appraisal of the Results of Surgically Treated Regional Ileitis. In: Lahey Birthday Volume. Springfield, Illinois, Charles C. Thomas, pp. 53-53, 1940.
8. Jordan, Sara M.: End Results of Radical Surgery of the Gastro-Intestinal Tract; as Seen by the Gastro-Enterologist. *J. A. M. A.*, 116:586-590, Feb. 15, 1941.

## Ulcerative Colitis---An Allergic Phenomenon<sup>\*</sup>

By

ALBERT F. R. ANDRESEN, M.D., F.A.C.P.  
BROOKLYN, NEW YORK

SO much has been written about so-called non-specific ulcerative colitis, or colitis gravis, in recent years, that it would seem superfluous to add to the accumulating literature on this subject. However, a careful study of the many articles shows such a wide divergence of opinion regarding the etiology and treatment of this disease that one wonders whether the various writers are discussing the same entity. Authors write with great conviction about infection caused by bacteria such as the colon bacillus, streptococcus, diplococcus, enterococcus and the bacilli of dysentery, while others, discarding a bacterial etiology, attempt to show that a virus is the etiological factor. While each writer stresses specific treatment for infection, actually we find that symptomatic treatment is depended upon for relief of symptoms. Non-specific therapy, artificial pyrexia, has been tried with some success, various emollients, adsorbents and sedatives have always been prescribed, and a careful diet has been insisted upon. The kind of diet recommended has varied radically with each author, stress in recent years however having been quite generally placed upon high vitamin and protein content. However, on studying the diets recommended as being most successful, we find one common factor, the limitation of the intake of milk or the entire elimination of milk products from the diet.

In a paper (1) read before this Association in 1925, on the subject of gastro-intestinal allergy, I included ulcerative colitis among allergic manifestations in the

gastro-intestinal tract and made suggestions regarding diagnosis and treatment of all gastro-intestinal allergic manifestations.

In 1933, D'Albora and I presented a paper (2) on ulcerative colitis before this Association, in which we stressed the importance of allergy as a cause of this disease and called attention to its successful treatment on this basis. And yet, although all other methods of treatment, including operation, have been given a thorough trial and found wanting, little attention has been paid to the allergic theory. In a series of fifty consecutive cases of severe ulcerative colitis treated on the gastro-intestinal service at the Long Island College Hospital in the past fifteen years, we had but two deaths, a mortality of four per cent, and these were caused by complications—one a mastoiditis with erysipelas, the other an acute pyelonephritis. And none of our cases has required operation for the ulcerative colitis. The severity of the disease may be judged by the fact that the longest duration before consulting us was twelve years, the shortest twelve days and the average fourteen months. Thirty per cent of the patients had had previous attacks, the average number being three. The average stay in hospital was forty days, the longest one hundred and twenty-nine days, the shortest eight days. Twenty-two patients were males, twenty-eight females and their average age was thirty years, varying from ten to fifty-one years. Seventy per cent were American born. In thirty-three of our cases (66%) food allergy was definitely demonstrated to be the cause of the disease and these were all successfully treated. In discussing the role of

<sup>\*</sup>From the Gastro-Enterological Service of Long Island College Hospital, Brooklyn, N. Y.

Read at the Annual Meeting of American Gastro-Enterological Association at Atlantic City, May 6, 1941.

allergy in the etiology of ulcerative colitis it is well to consider whether the theory of allergy will conform to what has been accepted as criteria of this disease.

### PATHOLOGY

The pathological lesions of ulcerative colitis have been quite definitely described and may occur in a part of the whole of the colon at one time. In the early stages hyperemia, hypersecretion and mucosal edema are present and a punctate rash, resembling herpes, is usually seen. As a result of localized ischemia, areas of necrosis develop and slough out, leaving ulcerated areas, which, when they coalesce, cause often extensive areas of denudation of mucosa, with small islands or tabs of mucosa still visible. These denuded areas may bleed upon slightest trauma or the actual laceration of small blood-vessels may produce more profuse bleeding. Very deep sloughing may produce single or multiple perforations, with resulting local or general peritonitis and later adhesions, deformities, kinks or obstructions. Induration, with infiltration by leucocytes, often demonstrable as eosinophiles, may disappear with healing or may result in fibrosis, with marked narrowing or stiffening of the colon. The mucosal lesions may disappear entirely, or with long-continued irritation, may result in polypoid changes, in which carcinoma may, but does not often, develop. More or less bacterial invasion may be found in the tissues, and lymphadenitis may be demonstrable in the mesenteric glands. Mackie has repeatedly called attention to the frequency with which the small intestine may show changes similar to those found in the colon, although some of the changes may be attributable to vitamin deficiency.

And now let us consider the changes caused by allergic reactions in the intestinal mucosa. Gray, Walzer, Harten (3, 4, 5) and their associates, in a series of reports of their experimental work in gastro-intestinal allergy, which has been twice reported to this Association by Gray, have demonstrated the macroscopic changes occurring in the sensitized mucosa of hemorrhoids and colostomies, and the microscopic changes in resected portions of sensitized intestinal mucosa of Rhesus monkeys during allergic reactions. The description of the pathological picture seen in these reactions is practically identical with the description of the early changes in ulcerative colitis, and it does not require any great stretch of the imagination to realize that repeated or continuous reactions of this type would result in the more severe lesions seen in the full-blown severe cases.

### SYMPTOMATOLOGY

The symptoms of ulcerative colitis also resemble allergic reactions elsewhere. As is the case in asthma or hay fever, an attack may frequently be started during or after some acute infection. This acute infection may be general, or distant in location, such as an attack of "grippe" or an acute upper respiratory or pelvic infection, or may be located in the gastro-intestinal tract, such as a "food poisoning" (*Salmonella* or *staphylococcus* infection), or even a bacillary dysentery. A damaged intestinal mucosa could conceiv-

ably become a locus for allergic reactions in an otherwise allergic individual.

The symptoms are readily explainable on the basis of the pathological findings. The irritation set up by the allergic reaction in the mucosa causes spasms and general hypermotility with resulting diarrhea and tenesmus. The number of stools may vary from one or two to twenty or thirty per day. The bleeding, sloughing and ulceration produce the typical stools of rectal discharges, containing blood, mucus, shreds of mucosa and, when infection has supervened, also pus. These rectal discharges may contain little fecal matter and there may be actual constipation in the presence of fifteen or twenty rectal discharges per day. Anorexia or actual disgust for food, resulting in insufficient intake, interference with digestive secretions, resulting in insufficient digestion, and incomplete absorption through the damaged intestinal mucosa over which contents are hurriedly propelled, combine to produce a picture of extreme emaciation and dehydration, with evidence of multiple food deficiencies. Symptoms of protein deficiency and of various vitamin and mineral deficiencies are often quite marked. Absorption of toxic materials from the extensively denuded areas, particularly if secondary infection has occurred, results in toxic symptoms, fever and glandular enlargements. The general exhaustion, the wear and tear on the nervous system and on the endocrine glands produce a neuropsychiatric problem often of major importance. These patients often do everything in their power to thwart the efforts of their attendants to help them, and in a ward will cause disturbance and hatred. Upon recovery the change in character is often almost unbelievable.

Complications will, of course, add to the gravity of the picture. In an emaciated, dehydrated patient the development of a mesenteric lymphadenitis, with severe pains and tenderness, temperatures reaching 104 or 105 F., and a marked leucocytosis, may simulate an acute abdomen, and the latter may actually be present if perforation has occurred.

### DIAGNOSIS

The diagnosis of ulcerative colitis should be made only after careful and complete study. The cardinal habit of calling every case of bloody diarrhea an ulcerative colitis and instituting treatment for this condition, without adequate proof that this is the true cause of symptoms, is tragic in its consequences. I venture to say that most gastro-enterologists see many more cases of bloody diarrhea due to carcinoma which have been treated for ulcerative colitis than they do of real ulcerative colitis. Polypoid changes in any part of the gastro-intestinal tract may produce symptoms similar to those we have discussed, as may tuberculosis, syphilis, lymphogranuloma venereum and regional enteritis. I have seen two cases of intussusception, due to colonic polyps, in which the symptoms had been ascribed to ulcerative colitis. Chronic hemorrhoids, organic or inorganic, may produce bloody diarrheas. The diarrhea of gastric or pancreatic origin, especially if associated with bleeding ano-rectal lesions,

may also cause confusion, and diarrheas due to psychic or endocrine disturbances must be ruled out. Dysenteries due to specific organisms should be early recognized so that specific treatments may be promptly instituted.

In making the diagnosis of ulcerative colitis, the *history* may be of help. The onset of symptoms may be gradual or may begin during an acute infection, as previously mentioned. In thirty per cent of our patients previous attacks had occurred, with intervals of freedom from symptoms. The individual or his family will often give a history of allergic manifestations in the gastro-intestinal tract or elsewhere. Symptoms referable to focal infections may be elicited. Psychic mal-adjustments may be discovered. The symptoms themselves may be mild or severe, often entirely independent of the severity of the lesions present in the bowel.

*Physical examination* should be complete and thorough. Abdominal examination may disclose nothing abnormal, may show distention, localized or general tenderness or rigidity and, at times, the thickened or spastic colon may be palpable and tender. General examination will usually show the presence of focal infections, may show evidences of allergic reactions in the skin or other parts of the body, and will, in severe cases, disclose the marked emaciation, dehydration and evidences of food, vitamin and mineral deficiencies already mentioned. It is important to ascertain at the start whether the patient has any organic lesions in any part of the body so that complications may be guarded against and treated early if they develop.

*Proctoscopic examination* is usually quite characteristic. In the early stage, marked redness and edema are present and there is considerable surface secretion and bleeding upon slight trauma, such as the touch of the proctoscope or cotton swab. A fine punctate rash, resembling skin herpes, is usually seen, the dots gradually enlarging, sloughing out and coalescing into a rash resembling eczema. In fully-developed cases the large areas of denudation, bleeding freely and almost continuously and the small shreds or islands of adherent mucosa, which often resemble and may later develop into polyps, are quite characteristic. In addition, the anal region may show hemorrhoids, fissures or fistula and the peri-anal skin may be indurated and eroded. The improvement in all findings when all foods to which the bowel is sensitized have been removed from the diet is so marked as at times to be almost unbelievable. Mucosa grows out from the small islands and rapidly covers the denuded areas, bleeding stops and in a few weeks an almost normal mucosa can be seen.

During the proctoscopic examination it is well to make smears directly from the diseased mucosa, to make immediate warm-stage examinations of scrapings from ulcerative areas, and, by means of long pipettes or syringes or long sterile swabs protected from contamination in sterile tubes, to get cultures directly from the sigmoid. Such examinations are obviously greatly preferable to mere examination of the stools or rectal discharges. Removal of biopsy

material may also be indicated. When parasitic infestation has been ruled out, the finding of eosinophiles in the exudate or scrapings from the mucosal lesions is very suggestive of allergy. Bacteriologic findings in our series of cases showed B Coli in ninety per cent of cases, in pure culture in forty per cent. Enterococci of various strains were found in sixty-two per cent of cases, probably due to their rapid progress preventing their usual destruction in the colon. In only six and two-tenths per cent of cases were they found in pure culture. Various strains of streptococci were cultured in fourteen per cent of cases, and staphylococci and B. proteus each in four per cent, but none of these were found in pure culture. Many other contaminating bacteria were also found at times. Specific dysenteries and amebic infestations were of course not included in our series.

*Roentgen examination* is very important and should not be confined to an opaque enema study. A careful gastro-intestinal series will not only show the marked intestinal hypermotility, but films taken at hourly intervals until the small intestine is empty will often disclose the irritability and mucosal thickening due to Vitamin B deficiency or the actual mucosal defects, induration and even partial obstructions indicating involvement of the small intestine in a process similar to that present in the colon. The highly irritable colon will not hold the barium meal, so that twenty-four and forty-eight hour films may show complete emptying unless complications such as partial obstruction, walled off perforation or diverticulation have occurred. However, when sensitization to milk is suspected, successive studies with and without milk in the barium meal may show a marked difference in the irritability of the whole tract. The gastro-intestinal series is also of great importance in ruling out other lesions. Even a cholecystographic study may be of value to rule out lesions of the biliary tract.

The opaque enema study, using both fluoroscopy and films, will usually show quite characteristic findings. In the early stages the general irritability, areas of spasm, lessening or disappearance of haustrations due to induration and the fuzzy appearance of the diseased mucosa are quite definite. When ulceration occurs, mucosal defects may be seen, producing a ragged appearance. With increasing fibrosis there is progressive narrowing of the lumen, until the colon resembles a garden hose, except that in some cases areas of more marked change may cause more severe narrowing, giving the colon the appearance of a string of sausages. Peritoneal irritation or involvement, due to deep penetration or actual walled-off perforations with pericolic exudates and adhesions, will show kinks or areas of immobility, and in very severe and prolonged cases, actual obstruction may have developed. Repeated Roentgenologic studies should be used to check the progress of a case and it is often surprising to see the improvement in all findings in a patient whose case is progressing favorably. Often a "garden-hose colon" will begin to show shallow haustrations within six or eight weeks and in six months or a year, especially in young patients, may be restored to a normal or almost normal appearance. At this stage the effect of ingested food to which a patient is sensitized or its addition to

the opaque enema may be used to demonstrate its marked effect on the Roentgenologic findings.

*Laboratory studies* are of importance. Examination of the stools or rectal discharges, will show the blood, mucus, mucosal shreds and pus mentioned before. Cysts or ova of parasites should be looked for, and undigested food particles should be noted. Although bacteriologic studies are best carried out primarily on specimens removed through the proctoscope, as previously mentioned, they may be continued on specimens of stools, thus avoiding repeated instrumentation. The effect of treatment on the flora may be checked, bacteriophages may be looked for and vaccines may be prepared. The improvement in the general appearance of the stools, the disappearance of blood and the gradual increase in consistency in cases under proper treatment is most gratifying.

*Gastric analysis* and examinations for pancreatic ferment activity are of value in ruling out lesions in these organs. In our ulcerative colitis cases only fifteen per cent showed an achlorhydria, twelve per cent a hypersecretion and seventy-three per cent showed normal gastric secretion. Where pancreatic ferment studies were made no very definite findings were recorded, although some diminution of pancreatic activity might be expected.

*Blood studies* are of interest. Serological examinations to rule out syphilis and lymphogranuloma venereum are important. Agglutination tests for dysentery and typhoid and paratyphoid groups are necessary in differential diagnosis. Blood counts in our fifty cases showed more or less anemia, depending upon the severity and particularly upon the duration of the disease. The using up of stored hematopoietic substances in prolonged bleeding and general depletion will, of course, produce the most profound and refractory anemias, and some of the anemias can also be attributed to vitamin deficiency. In our series the average red blood cell count was about four million, the highest five million, the lowest three million. Hemoglobin estimations averaged seventy per cent, with a low of forty-five per cent and a high of ninety per cent. There was a moderate leucocytosis in many cases, averaging ninety-eight hundred leucocytes, but one patient showed but thirty-seven hundred cells and one, with secondary infection, reached nineteen thousand five hundred. Eosinophilia, so suggestive of allergy when parasitic infestation can be ruled out, was not uniformly outstanding, the average being, however, five per cent, with a high of seventeen per cent and a low of two per cent of eosinophiles. Chemical studies of the blood revealed no constant abnormalities, even the calcium and phosphorus determinations showing consistently normal findings. Blood calcium in our group varied from 8.8 to 11 mg. per 100 cc. and averaged 9.6, blood phosphorus, from 3. to 5.5, averaging 4.2 mg. per 100 cc. Individual complicated cases showed occasional acidosis, hypochloremia or other abnormalities. Vitamin deficiencies were at times demonstrated in blood and urine. Prothrombin determinations showed little if any variation from the

normal. Other laboratory examinations may be made use of as indicated.

### ALLERGY STUDY

In the absence of indications that some specific organism is the direct cause of the ulcerative colitis, and even when such organisms have been found and may be thought to be playing an important role in the etiology and prolongation of the process, it is well to conduct a study to determine whether allergy is the prime or contributing cause. It is not sufficient to have some dermic, intradermic, patch or even passive transfer tests performed and to dismiss the case as not allergic in origin because no conclusive findings are observed or because too many reactions are encountered, as is so often done. Early in our experience with the skin tests for allergy we realized their futility in determination of the causes of the gastro-intestinal manifestations of food allergy and it is over ten years since we abandoned them altogether. Even bacterial allergy cannot be accurately shown by skin tests, and sensitivity to internal secretions or hormones is usually suspected from the relation of symptoms to endocrine activity or to menstrual or other functions. It is also known that manifestations of allergy in general may be initiated or may disappear at a time of endocrine imbalance, as at puberty, pregnancy, lactation or the menopause and may be related to activity at sites of focal infection, such as acute upper respiratory, pelvic or gastro-intestinal infections. Ten of our patients showed a subsidence of their ulcerative colitis following removal of badly infected tonsils.

*Food allergy* having been found to be the principal cause of the ulcerative colitis in thirty-three of our patients, or sixty-six per cent of the total, it is important to realize that a determination of the food or foods to which the patient is sensitized is of immediate importance in the study of any case. Milk having been found to be an offending food in eighty-four per cent of our cases, and the only one in nearly forty per cent of the cases, the immediate elimination of milk and all milk products from the diet will frequently result in a dramatic improvement in symptoms and will thus help to confirm milk as a primary cause of the disease, permitting further and more careful search for other offending foods in a more leisurely fashion. The diary method of study for food allergy and even the use of the so-called elimination diets is not applicable to such a severe condition as ulcerative colitis. If foods are the cause of the disease, it is obvious that to produce such severe lesions the foods must have been taken practically every day and in fairly large quantities, although others taken only occasionally might be contributing factors. Foods commonly taken every day may therefore be suspected in any case, and these include milk, egg, wheat, potato, orange and tomato. In our thirty-three cases, in addition to the eighty-four per cent showing sensitivity to milk, eighteen per cent were allergic to wheat, fifteen per cent to tomato, twelve per cent each to orange and potato and only nine per cent to egg.



In studying gastro-intestinal allergy in general we have been using a diet we call Allergy Test Diet No. 1 for a number of years, and this contains the first five of the foods mentioned, distributed through the day as follows:

#### ALLERGY TEST DIET NO. 1

*5 Foods:* Milk, Egg, Wheat, Potato, Orange

*Breakfast:* milk, egg, wheat cereal and cream, wheat bread and butter and orange

*Lunch:* milk, egg or cheese, potato, bread and butter, dessert (orange-flavored custard or wheat pudding or whole orange)

*Supper:* Same as lunch or breakfast.

Between meals and at bedtime: milk with cream and glucose and wheat crackers.

This diet resembles the soft, non-residue type of diet so often used in ulcerative colitis. In severe cases the use of this diet, which might cause a marked exacerbation of symptoms, would be contraindicated, but in mild cases, such an exacerbation would show that among the five foods in this diet were ones responsible for the disease. Elimination of one at a time, beginning with milk, until the symptoms begin to show marked improvement, would then aid in the determination of the offending foods, which can later be checked individually by watching the effect of their administration when symptoms have cleared up. The addition of one new food each day thereafter and watching the effect can then be used to determine other food allergens. It is well to be careful to add at first foods of high nutritive value.

However, in severe cases or in patients who have shown an exacerbation when placed on Diet No. 1, it is often expedient to give a diet containing five foods, none of which is contained in the first diet, as follows:

#### ALLERGY TEST DIET NO. 2

*5 Foods:* Gelatin, Rice, Rye, Peas, Raspberry (or other vegetable or fruit)

*Breakfast:* boiled rice, Rye Krisp, Gelatin drink, raspberries

*Lunch:* peas, rice, Rye Krisp, Gelatin drink, raspberries

*Supper:* Same as lunch or breakfast.

Between meals and at bedtime: Gelatin drink and Rye Krisp.

The Gelatin drink is made by adding a teaspoonful of powdered gelatin to a fruit juice made of the fruit or berry used in the diet, sweetened and fortified with glucose.

The various items in this diet must be varied to suit the individual's needs, avoiding foods suspected of causing symptoms. Occasionally one meat is used for the protein ration. If this diet contains no food to which the patient is sensitized, improvement will often be quite startling, all symptoms beginning to subside markedly within even a day or two, so that additions may be made to the diet within a short time, checking and re-checking foods suspected of causing exacerbations. Rarely must some foods be eliminated and tried again as outlined above. This diet study can be instituted on the first day of the general study, so that

no time is wasted in the complete survey of the case, and the patient's condition may often be already much improved by the time all examinations have been completed. When the study is complete the patient must be provided with a list of the foods known to cause symptoms and it must be explained to the patient that new foods may from time to time have to be tested and if found bad, to be added to the list.

#### TREATMENT

In the emaciated, anemic, dehydrated and perhaps acidotic patient with a severe ulcerative colitis, the first indication is for *general treatment*, with rest, both physical and mental, and the administration of fluids, preferably parenterally. Blood or plasma and later glucose and saline solutions, to which cevitamic acid has been added, should be used intravenously, the quantity being governed by the consideration of restoring and maintaining the water-balance of the tissues. Until there is an assurance that vitamins are being absorbed from the gastro-intestinal tract in adequate amounts, their parenteral use is also indicated, and iron, calcium, potassium or other minerals may also be given as indicated. Endocrine preparations, especially epinephrine, pituitrin or parathyroid hormone, may be of considerable value in some cases, as they are in other allergic states. General hygienic care, fresh air, sunshine or ultraviolet radiation, oral hygiene and the removal of focal infections are definitely indicated.

*Symptomatic treatment*, including the use of sedatives or antispasmodics, antiseptics, emollients and coagulants, the care of rectal or skin lesions, and psychologic management, is also to be stressed, especially in the early stages of treatment. Oil or gelatin enemas, the latter acting also as coagulants, may help to soothe the irritated rectal mucosa. In our experience the use of astringent or antiseptic instillations, insufflations, enemas or irrigations, has been of no value, even very often causing a marked irritation, with exacerbation of symptoms.

*Immunologic treatment*, the use of vaccines, sera, bacteriophages or filtrates may be used where indicated, although in our experience artificial pyrexia, by means of intravenous injections of foreign protein, electric cabinets or even hot baths has often been of as much or greater value. The febrile reaction would, of course, be also of value in allergic states.

*Surgical treatment* for the ulcerative colitis itself has not been necessary in any of our cases, although occasional operations were performed for hemorrhoids, fissures or fistulae. One patient required two operations for closure of a previously performed appendicostomy. The removal of a part or of the whole of the colon during acute symptoms would seem to be a too formidable procedure, and the establishment of stomata for drainage, or local treatment is not logical. When a colon can show the amount of improvement in a short period of time, when the patient's general condition can be built up in such an excellent manner by means of the treatment we have repeatedly outlined, why should a patient's gastro-intestinal tract be crippled by the operations which are now so casually being recommended? However, acute perforation



would, as elsewhere, be a definite indication for operation, and if, in an unusually prolonged case, healing of the deeper lesions leaves a colon crippled or obstructed by cicatrices or adhesions, producing obstructive symptoms or intractable diarrheas, operation may have to be performed.

*Dietetic treatment* is of the greatest importance and must take into consideration that digestive secretions may be deficient, that the hypermotility is carrying intestinal contents along at an abnormal speed, and that the irritated denuded mucosa is incapable of normal absorption. To overcome the multiple food deficiencies and to improve and maintain general nutrition, it is therefore necessary to give foods in concentrated, easily digestible or predigested forms at frequent intervals, being sure that there is an adequate protein content and that sufficient vitamins are being provided. It is usually necessary to fortify the diet by giving vitamin concentrates orally or parenterally, extra minerals may be added as indicated, and fluids sufficient to restore and maintain the fluid balance must be given orally and often parenterally. As soon as the foods to which the patient is sensitized have been discovered, a suitable diet can be planned, avoiding known allergens. Fruits and vegetables, raw and cooked, are valuable for their vitamin-containing and bulk-producing characteristics and are not irritating if they have been found not to include ones to which the patient is known to be allergic. Meats, liver, liver extracts, gelatin and eggs should provide an adequate protein ration. Fats may be a problem in milk-sensitive individuals, as in many of these cases even minute quantities of cream or butter and even the milk in bread may cause exacerbation of symptoms. In such cases oils or animal fats must be provided. Dextrose is of value in that its lower sweetening power makes it possible to use large quantities in the preparation of foods and thus raise their caloric value. No standard diet can be recommended, as each individual case must have its diet separately planned. However, starting with one of the allergy diets mentioned above, additions can be made from day to day, bearing in mind the principles just mentioned.

*Desensitization* to foods to which the patient is sensitized should not be attempted until all symptoms have long since disappeared and the bowel has resumed a normal appearance. Only foods which are taken daily in an ordinary diet are suitable for this procedure. By beginning with minute quantities by mouth (for instance, one drop of milk) and gradually increasing the amount each day, some degree of desensitization may be accomplished, although practically never can a patient reach a point where unlimited quantities can be taken. And it must be remembered that failure to continue with daily rations of the foods will rapidly result in a return of the sensitivity.

### PROGNOSIS

Ulcerative colitis has always been considered not only a difficult disease to treat successfully, but the tendency to recurrence has always made the prognosis rather poor. The mortality has been considered high and this has been further increased by surgical

attack. In our series of fifty consecutive cases, all with definitely severe lesions, we have had only two deaths—a mortality of four per cent, and neither of these patients died directly as a result of the disease. One patient died of a streptococcus hemolyticus mastoiditis, with erysipelas and brain involvement, the other succumbed to a severe pyelonephritis. None of our patients developed sufficiently severe complications to require operative interference. Ten patients who had tonsillectomies performed, showed marked improvement soon thereafter, and have had no severe recurrences. Eight patients have returned to the hospital with subsequent exacerbations, onset of which could be traced to acute upper respiratory infections or to indulgence in foods to which the patients knew they were sensitized. In general, the prognosis, as in the case of asthma and other allergic conditions, cannot be expressed as good or bad. Allergy, the nature and cause of which is not known, is not a curable condition. There is always a tendency to recurrence of allergic reactions, not only in the same location but in other tissues of the body. Patients may develop asthma or hay fever at one time, urticaria or eczema at another and gastro-intestinal allergic manifestations at another, or all of these lesions may occur simultaneously. The same food may produce manifestations in different tissues or each region may be sensitive to different foods. And besides this, patients are constantly acquiring new sensitivities and perhaps losing former ones. A patient, therefore, who reports after a year that he is still following his old diet and cannot understand why he is then having a recurrence of symptoms, simply has not grasped the situation in regard to allergy. No diet for an allergic individual can ever be static—changes are being made from time to time as study continues and severe reactions thus avoided. In an intelligent patient, under careful though not necessarily close supervision by a clinician familiar with allergic problems, the prognosis in ulcerative colitis can be said to be decidedly favorable, not only in regard to restoration of a well-functioning colon, but in regard to the danger of severe exacerbations.

### SUMMARY

1. Ulcerative colitis is frequently due to food allergy—in at least sixty-six per cent of cases.
2. The resemblance between the mucosal lesions of ulcerative colitis and allergic reactions in the skin is quite obvious.
3. The pathological findings in early ulcerative colitis are identical with those demonstrated in allergy experiments in humans and animals. Their progression would produce the severe, later lesions.
4. The symptoms of ulcerative colitis are easily explainable on an allergic basis.
5. Proctoscopic and roentgenological examinations can be used to demonstrate the effect of allergenic foods and the improvement on their withdrawal from the diet.
6. Treatment based on allergic considerations has produced results which are better than those based entirely on an infective etiology.

## REFERENCES

1. Andresen, A. F. R.: *Med. J. and Record*, cxvll, No. 5, pp. 271-275, Sept. 2, 1925.
2. Andresen, A. F. R. and D'Albora, J. B.: *Med. Times and Long Island Med. J.*, Oct., 1933.
3. Gray, I. and Walzer, M.: *J. Dig. Dis. and Nutrit.*, 14, No. 11, Jan., 1938.
4. Walzer, M., Gray, I. and Harten, M.: *Ann. Int. Med.*, Vol. 13, No. 11, May, 1940.
5. Walzer, M., Gray, I., Straus, H. W. and Livingston, S.: *J. Immunol.*, xxxiv, 91, 1935.

## DISCUSSION

IRVING GRAY (Brooklyn, N. Y.): The presentation by Dr. Andresen was stimulating and interesting. The etiology of non-specific ulcerative colitis still remains a matter of discussion. In collaboration with Dr. Matthew Walzer and his associates, we have studied the mechanism of the induced allergic reactions of the mucous membrane of the gastro-intestinal tract, both in the human and in the Rhesus monkey. Our first studies dealt with the allergic reactions in the mucous membrane of the rectum in humans. After sensitization of the rectal mucous membrane with human serum containing atopic reagins a local inflammatory reaction was subsequently induced by feeding of the specific related protein. The antigen, after absorption from the gastro-intestinal tract, reached the sensitized site by way of the general circulation within a period of 10 to 15 minutes as a rule. The allergic reaction was characterized by marked edema, erythema and mucous secretion. By this same technic of passive local sensitization, induced allergic reactions were studied in the ileum and colon of humans who had had ileocolostomy and colostomy procedure. The tremendous edema of the mucous membrane obtained in these studies has been demonstrated to us this morning on the screen by Dr. Andresen. The allergic reaction of the mucous membrane lasted approximately one hour.

The mucous membrane of the gastro-intestinal tract has long been recognized as a shock tissue. It has further been known that the atopic reagin may be fixed in any shock tissue of the body. If the atopic reagin is fixed in the mucous membrane of the colon it is reasonable to conceive that the allergic and inflammatory reaction in the mucous membrane of the colon can occur when excited by the specific antigen.

Dr. Andresen has shown that certain foods, especially milk, were antigenic in many of his patients. The question may be raised as to the possibility of bacterial allergy in non-specific ulcerative colitis.

Our experimental studies have shown that the allergic reaction, after sensitization, can be induced in the mucous membrane of any portion of the gastro-intestinal tract of the Rhesus monkey and that these reactions are essentially the same as those observed in the rectum, ileum and colon of humans. The local allergic reaction at the site of sensitization was induced either by direct topical application or by ingestion or after intravenous injection of the specific protein. Histological studies of the tissue, removed after the allergic reaction was induced in the monkey showed a marked edema two to eight times the normal tissue thickness of the submucosa with cellular infiltration. One may reasonably assume with the human colon in situ that if this organ is the seat of an allergic reaction that the marked inflammatory edema as a result of allergic response may produce symptoms such as diarrhea. If there are repeated attacks of these allergic reactions in the mucous membrane of the colon secondary infection may develop at the site of reactions and a non-specific ulcerative colitis may develop.

In the cases we have treated a thorough personal and familial history of atopy has been sought. My information has failed to reveal any special incidence of allergy in non-specific ulcerative colitis.

DR. T. T. MACKIE (New York, N. Y.): Mr. President, I think that it is very unfortunate that Dr. Andresen should have described the factor of allergy in ulcerative colitis as long ago as 1924 or 1925, and that that report, which is in the literature, has been completely ignored by almost everyone working in this field.

I say I think it is unfortunate, because we are convinced of the fundamental importance of this factor in the progression and maintenance of activity of the disease. Our experience does not indicate to us, however, that the allergy is a primary factor; in other words, it appears to be a local sensitization developing secondarily upon a tissue which has previously become inflamed as the result of some other factor.

We have studied in all a total of two hundred cases whom we have followed under continuous observation through at least one cycle of the disease. Of these two hundred cases, at one time or another in their course we have obtained good evidence of allergy on the basis of symptoms, and the appearance at proctoscopy in response to successive addition and withdrawal of suspected foods, in approximately 60 per cent of all individuals.

It is important, however, to realize that if one divides the cycle of the disease into four phases, as follows: Phase 1, of acute activity; Phase 2, of convalescence; Phase 3, of quiescence, and Phase 4, of early recurrence; that the probability of getting good evidence of an allergy varies enormously.

Of those yielding such evidence the approximate figures are as follows: In Phase 1, 70% are positive. In Phase 2 only 10%; in Phase 3, 2%, and in Phase 4, 18%.

This variation of incidence rate reveals the magnitude of the problem in terms of time and demonstrates the necessity of studying these individuals carefully and repeatedly throughout at least one complete cycle of the disease. Furthermore, we are in complete agreement with Dr. Andresen concerning the utter failure of any of the skin test methods. Duplicate studies on a significant group have failed to reveal any parallelism between the evidence obtained by skin tests and that afforded by test diets.

DR. PHILIP W. BROWN (Rochester, Minn.): Mr. President, I should like to ask Dr. Andresen if I am clear on this point that sensitivity or allergic reaction is a factor or a cause in the production of ulcerative disease that we call ulcerative colitis?

It has seemed to me that there is no question that the sensitivity to foods will contribute to an exacerbation of the symptoms. I am interested in the high percentage of patients who react to milk, 84 per cent.

The problem that occurs to me is that there is a higher incidence of people that become worse from lack of food than because we give them enough food, although it is not a question of discounting or refusing to accept the fact that allergy may contribute. On the other hand, malnutrition contributes considerably, and intercurrent infections are the biggest factor in exacerbations. Maybe that is allergic. Also, we know that psychic trauma may have an influence.

I am interested to hear Dr. Andresen and Dr. Mackie emphasize the lack of value of skin tests for foods. Certainly in the hands of any but those who are highly informed and very intelligent and conscientious, it seems to me a great deal more damage comes from the elimination of too many items of food, to the point where the patient is all but eliminated, and I think we must be cautious in this respect.

DR. Z. BERCOVITZ (New York City): Mr. President, Members and Guests: I wish to take this opportunity to express my appreciation to Dr. Andresen for a sensible régime that he has outlined in the treatment of ulcerative colitis. I am heartily in accord with it.

I feel that too frequently there have been those who have become overenthusiastic about some chemotherapeutic agent or some other agent which has clouded their thinking so that they have not been able to see through to the real problem, that we must treat the patient and not his bacteria; that we must not treat his viruses or his vitamins but the patient as a whole; and Dr. Andresen has very definitely outlined that.

I am impressed, as I have been for a long time, with Dr. Andresen's work on allergy and in our studies of cellular exudates and bowel discharges for a number of years we have been seeing cells that we have questioned with reference to the matter of their being eosinophiles.

I might say that it has taken the past four or five years to develop a technic whereby we can demonstrate eosinophiles satisfactorily. It is fundamental that the smear be kept wet through the entire process because if it is allowed to dry at all, the cells disintegrate so that they are unrecognizable; but I think it will be possible within the next few weeks to publish our reports on the newer technic whereby we are quite constantly able to demonstrate eosinophiles in the bowel discharge, and in making smears from the bowel discharge and bowel mucosa, this will help a great deal.

I wish to add my word to what has been said previously in regard to the inadequacy of chemotherapy and sulfanyls. We have found, as Dr. Crohn has said, that it does not either sterilize the bowel or cure chronic ulcerative colitis. We have even seen unfortunate reactions from sulfanyl-quanidine. No drug of this sort will cure a patient with irreversible changes in the bowel wall.

DR. ALBERT F. R. ANDRESEN (Brooklyn, N. Y.) (closing the discussion): Mr. President, I am very grateful for the comprehensive discussion which my paper brought out, but regret that there were no more criticisms to be answered. I again thank Dr. Gray for permitting me to use the slides which illustrated some of the very fine research work in allergy which he and his companions have been carrying on so successfully. The question of whether infection plays a part in the original production of the ulcerative lesions in the colon is an interesting one. I believe that the allergic reaction occurs first and is often followed by bacterial invasion of the damaged tissues. The infection adds to the severity of the reaction, but does not necessarily interfere with the restoration of a

fairly normal mucosa afterwards. On the day before I came here I met a former patient, a dental student, whom I had not seen since he left the hospital eighteen months ago. For the first two or three weeks of his hospital stay he was practically moribund, with an almost constant bloody rectal discharge. He had many transfusions and intravenous glucose and vitamin injections. He was found to be so sensitive to milk that when later we tried to desensitize him seven minims of milk produced a violent exacerbation of bloody diarrhea and a marked reaction in his rectosigmoid mucosa, which only a few days before had looked practically normal. Since leaving the hospital he had gained seventy pounds, had successfully continued with his dental studies and had only one or two formed or occasional soft stools per day except for a few exacerbations of diarrhea on occasions when he tried to eat milk-containing foods, such as ice cream, potatoes, au gratin or puddings.

It is interesting to note that Dr. Mackie's percentage of ulcerative colitis cases found to be definitely due to allergy is almost exactly the same as ours—he reports 63 per cent, we reported 66 per cent. I repeat that I see no reason why the allergic reaction cannot be the primary lesion in the bowel. Even where the disease follows an acute infection, in the gastro-intestinal tract or elsewhere, the bowel mucosa may become sensitized as a result of this infection, just as hay fever and asthma often follow acute infections. Seasonal variations in sensitivity have been noted in other parts of the body as well as in the gastro-intestinal tract, and may be due to various factors, including the effect of sunshine on calcium metabolism, which affects allergic conditions. In the case of milk sensitivity the seasonal variation may be due to changes in the diet of the cow, the patient being sensitive to some particular article in that diet.

I am very much pleased that Dr. Bercovitz has devised a simple way to recognize eosinophiles in the rectal discharges. I am sure that this will be a great help in adding another link to the chain of evidence proving the allergic origin of ulcerative colitis. I am glad that Dr. Bercovitz again has emphasized the importance of the care of the patient as a whole and not only of his local condition. It is only by careful study and treatment of every part of the patient's system that we can hope for results in any gastro-intestinal disease.

## The Enzymatic Activity of Duodenal Juice and Blood Serum of Patients With Atrophy of the Gastric Mucosa

By

A. M. SERBY, M.D.\*

and

FREDERICK REICH, Ph.D.†

CHICAGO, ILLINOIS

THE frequency with which atrophic gastritis is now being found either as a primary disease or in association with other diseases has given rise to much speculation. Gradually other organs besides the stomach, and other physiological functions are being investigated to see if light can be thrown on the origin of the gastritis. It occurred to the authors that it

might be worthwhile in these cases to look for changes in the external secretion of the pancreas. Some patients with atrophic gastritis are subject to intermittent periods of diarrhea. It was considered possible that the pancreas might be made atrophic or its function might be depressed by the same toxin or antitoxins that had caused the gastric change.

### METHOD

Pancreatic flow was stimulated by the intraduodenal introduction of 10 per cent oleic acid throat

\*Assistant of the Department of Medicine, Michael Reese Hospital.  
†Research Associate in the Department of Immunology, Michael Reese Hospital.  
Received August 1, 1941.

Miller Abbott tube (1). Fluid was collected for thirty minutes, and chemical estimation of lipase and trypsin was made within one hour. Simultaneously, venous blood was drawn for lipase determination.

### STUDIES

Twenty-two consecutive patients with pertinent clinical and gastroscopic findings were studied. The ages ranged from thirty-one to sixty-eight. Eighteen patients were females and four were males. Free gastric acid was present in fifteen and absent in seven.

In seven patients the typical picture of uncomplicated atrophic gastritis was found, and in fifteen, other diseases such as hypochromic anemia, psychoneurosis, chronic hypertrophic arthritis, chronic allergic sinusitis, hay fever, chronic cholecystitis, C. N. S. syphilis, neurosis, duodenal ulcer, early menopause, and hypertension were present.

The symptoms corresponded closely to the syndrome as described by Schindler and others (2 and 3). In fact, some of these patients were gastroscoped because the clinical symptoms suggested the presence of atrophic gastritis.

**Controls.** Ten normal individuals, ranging in age from sixteen to thirty-six years, and one aged fifty-seven, were studied. Seven were males and three were females.

**Findings.** A comparison of the lipase and trypsin in the duodenal contents of ten normal persons and twenty-two patients with atrophic gastritis revealed no significant differences. A comparison of the lipase in the sera of ten normal persons and twenty-two patients with atrophic gastritis revealed no significant differences.

### CONCLUSIONS

No significant deviations from normal were noted in a study of lipase and trypsin in the duodenal contents of twenty-two patients with atrophy of the gastric mucosa. No significant deviations were noted in the blood lipase in the same group.

**Note:** Lipolytic activity of the fluids was determined by the method of Kaplan, Cohn and Reich (unpublished). Tryptic activity was determined by the method of Anson and Mirsky (4).

Thanks are extended to the Department of Gastro-Intestinal Research, Michael Reese Hospital, for help and advice.

### REFERENCES

1. McClure, C. W., Mendenhall, W. L. and Huntsinger, M. E.: Studies in Liver Function IV. A Procedure for the Uniform Stimulation of Biliary Flow. *Bost. Med. and Surg. J.*, 193:1052, 1925.
2. Schindler, R., Ortmyer, M. and Renshaw, J. F.: Clinical Symptoms of Chronic Gastritis. *Arch. Int. Med.*, 60:143, 1937.
3. Schindler, R. and Murphy, H. M.: Symptomatology of Chronic Atrophic Gastritis. *Am. J. Dig. Dis.*, 7:7-13, 1940.
4. Anson, M. L. and Mirsky, A. E.: The Estimation of Trypsin with Hemoglobin. *J. Gen. Physiol.*, 17:151, 1933.

## Free Tyrosin in the Blood Filtrate as an Indication of Liver Disease\*

By

I. R. JANKELSON, M.D.

BOSTON, MASSACHUSETTS

**C**ONSIDERING the numerous liver function tests described, relatively few survived the test of time. Many have been forgotten and abandoned because they were found unsatisfactory and wanting as too complicated, non-sensitive, not specific, unreliable, or non-contributory. Others like the galactose, bromsulphthalein and hippuric acid tests have been shown to be of value in the investigation of liver disease. However, no one test permits a conclusion as to all liver functions.

Although all liver functions are important in the body economy, one of its most essential ones is the intermediate protein metabolism. Many tests to determine this function of the liver have been proposed, like urea and ammonia urinary excretion, the amino acids in the blood and urine, the creatin and creatinin in the urine and blood. For various reasons, the discussion of which would lead one far astray, all of them were found more or less unsatisfactory and as such have been largely abandoned. Since in liver disease not all its functions are equally affected, it becomes apparent that a specific, sensitive and simple test for protein metabolism of the liver is of importance. With this in view, the present author and his co-workers have proposed the determination of

the free tyrosin in the blood filtrate as a liver function test.

Tyrosin as well as leucin crystals in the urine of patients with acute yellow atrophy of the liver were described by Frérichs (1). However, they appear only in about half of the cases of liver atrophy but also in other severe liver injuries (Eppinger and Walzel (2)). A more sensitive test for tyrosin in the urine is the tyrosinase method described by Lichtman and Sobotka (3). Neuberg and Richter (4) in a case of acute yellow atrophy of the liver demonstrated tyrosin among other amino acids in the blood. The technique used in our studies differed from that described by the above observers and is relatively simple. It was described in detail in a previous communication (5) and hence is omitted here. Suffice it to say, that it determines quantitatively (in terms of one to three plus) the free tyrosin in the blood filtrate.

In order to determine the specificity of this test studies were made on normal controls and in disease of the liver and other organs. In 20 young healthy individuals, free tyrosin was not found in the blood filtrate either after an overnight fast or 3 to 4 hours after breakfast. In 274 hospital cases, involving disease of almost every system, but not including liver disease, tyrosin was not demonstrated in the blood filtrate after an overnight fast. These patients suffered from a variety of diseases including cardio-vascular,

\*From First and Third (Tufts) Medical Services, Boston City Hospital.

Aided by the Charlton fund of Tufts College Medical School.  
Read at the Annual Meeting of the American Gastro-Enterological Association at Atlantic City, N. J., May 6, 1941.

would, as elsewhere, be a definite indication for operation, and if, in an unusually prolonged case, healing of the deeper lesions leaves a colon crippled or obstructed by cicatrices or adhesions, producing obstructive symptoms or intractable diarrheas, operation may have to be performed.

*Dietetic treatment* is of the greatest importance and must take into consideration that digestive secretions may be deficient, that the hypermotility is carrying intestinal contents along at an abnormal speed, and that the irritated denuded mucosa is incapable of normal absorption. To overcome the multiple food-deficiencies and to improve and maintain general nutrition, it is therefore necessary to give foods in concentrated, easily digestible or predigested forms at frequent intervals, being sure that there is an adequate protein content and that sufficient vitamins are being provided. It is usually necessary to fortify the diet by giving vitamin concentrates orally or parenterally, extra minerals may be added as indicated, and fluids sufficient to restore and maintain the fluid balance must be given orally and often parenterally. As soon as the foods to which the patient is sensitized have been discovered, a suitable diet can be planned, avoiding known allergens. Fruits and vegetables, raw and cooked, are valuable for their vitamin-containing and bulk-producing characteristics and are not irritating if they have been found not to include ones to which the patient is known to be allergic. Meats, liver, liver extracts, gelatin and eggs should provide an adequate protein ration. Fats may be a problem in milk-sensitive individuals, as in many of these cases even minute quantities of cream or butter and even the milk in bread may cause exacerbation of symptoms. In such cases oils or animal fats must be provided. Dextrose is of value in that its lower sweetening power makes it possible to use large quantities in the preparation of foods and thus raise their caloric value. No standard diet can be recommended, as each individual case must have its diet separately planned. However, starting with one of the allergy diets mentioned above, additions can be made from day to day, bearing in mind the principles just mentioned.

*Desensitization* to foods to which the patient is sensitized should not be attempted until all symptoms have long since disappeared and the bowel has resumed a normal appearance. Only foods which are taken daily in an ordinary diet are suitable for this procedure. By beginning with minute quantities by mouth (for instance, one drop of milk) and gradually increasing the amount each day, some degree of desensitization may be accomplished, although practically never can a patient reach a point where unlimited quantities can be taken. And it must be remembered that failure to continue with daily rations of the foods will rapidly result in a return of the sensitivity.

### PROGNOSIS

Ulcerative colitis has always been considered not only a difficult disease to treat successfully, but the tendency to recurrences has always made the prognosis rather poor. The mortality has been considered high and this has been further increased by surgical

attack. In our series of fifty consecutive cases, all with definitely severe lesions, we have had only two deaths—a mortality of four per cent, and neither of these patients died directly as a result of the disease. One patient died of a streptococcus hemolyticus mastoiditis, with erysipelas and brain involvement, the other succumbed to a severe pyelonephritis. None of our patients developed sufficiently severe complications to require operative interference. Ten patients who had tonsillectomies performed, showed marked improvement soon thereafter, and have had no severe recurrences. Eight patients have returned to the hospital with subsequent exacerbations, onset of which could be traced to acute upper respiratory infections or to indulgence in foods to which the patients knew they were sensitized. In general, the prognosis, as in the case of asthma and other allergic conditions, cannot be expressed as good or bad. Allergy, the nature and cause of which is not known, is not a curable condition. There is always a tendency to recurrence of allergic reactions, not only in the same location but in other tissues of the body. Patients may develop asthma or hay fever at one time, urticaria or eczema at another and gastro-intestinal allergic manifestations at another, or all of these lesions may occur simultaneously. The same food may produce manifestations in different tissues or each region may be sensitive to different foods. And besides this, patients are constantly acquiring new sensitivities and perhaps losing former ones. A patient, therefore, who reports after a year that he is still following his old diet and cannot understand why he is then having a recurrence of symptoms, simply has not grasped the situation in regard to allergy. No diet for an allergic individual can ever be static—changes are being made from time to time as study continues and severe reactions thus avoided. In an intelligent patient, under careful though not necessarily close supervision by a clinician familiar with allergic problems, the prognosis in ulcerative colitis can be said to be decidedly favorable, not only in regard to restoration of a well-functioning colon, but in regard to the danger of severe exacerbations.

### SUMMARY

1. Ulcerative colitis is frequently due to food allergy—in at least sixty-six per cent of cases.
2. The resemblance between the mucosal lesions of ulcerative colitis and allergic reactions in the skin is quite obvious.
3. The pathological findings in early ulcerative colitis are identical with those demonstrated in allergy experiments in humans and animals. Their progression would produce the severe, later lesions.
4. The symptoms of ulcerative colitis are easily explainable on an allergic basis.
5. Proctoscopic and roentgenological examinations can be used to demonstrate the effect of allergenic foods and the improvement on their withdrawal from the diet.
6. Treatment based on allergic considerations has produced results which are better than those based entirely on an infective etiology.



were examined and no free tyrosin found in the filtrate. However, in 3 cases a trace (+) of free tyrosin was found in the blood filtrate without any clinical evidence of a hepatitis. In one case of neo-arsphenamin jaundice free tyrosin (+ + +) was found in the blood filtrate. Six patients with heart disease in the stage of marked decompensation were also examined. No free tyrosin was found in the blood filtrate. In a case of cardiac cirrhosis of the liver free tyrosin (+ + +) was found on several examinations.

### DISCUSSION

The demonstration of free tyrosin in the blood filtrate in a fasting state indicates with few exceptions liver disease. Tyrosinemia occurs in diffuse liver damage more frequently than in cases of focal disease. Like all functional studies of liver, this test has definite limitations. First, and foremost, is the "factor of safety" in the liver. Even in the presence of considerable liver cell destruction any and all functional tests may be negative. Thus, positive findings were shown in only 80 to 85 per cent of diffuse liver damage and negative tests were even more frequent in circumscribed disease, like gumma, cancer metastasis, and in obstructive jaundice. Moreover, as a rule in diffuse liver damage higher amounts of free tyrosin are shown in the blood filtrate. The tyrosinemia more or less parallels the liver damage, as has been shown in the cases of obstructive jaundice and hepatitis. However, the absence of free tyrosin in the blood filtrate does not exclude either diffuse or focal liver damage.

Still further complicating all liver function tests, including the one under discussion here, is the great regenerative power of the liver. Obviously, during the stage of repair in spite of anatomic lesions, the functional capacity may be restored and liver function tests therefore, may become negative. Actually, it was observed in this study that the amount of free tyrosin in the blood filtrate diminished in the recrudescence stages of acute hepatitis and often disappeared before the jaundice cleared. Thus, repeated observations may be of prognostic significance. On the other hand, in obstructive jaundice, where liver damage develops as a result of prolonged back pressure upon the liver, the amount of tyrosin in the blood shows a tendency to increase. In this way, by

repeated tyrosin estimations in jaundiced patients, some evidence as to the cause of the jaundice may be obtained. In the vast majority of chronic gall bladder disease no free tyrosin appeared in the blood filtrate. Nor can it be demonstrated in other digestive tract diseases.

These observations attest the specificity of the study of free tyrosin in liver disease. The test is simple and can be performed by an experienced technician with accuracy and does not require unusual equipment or facilities.

Liver function tests are employed to determine the presence of liver disease, are used in differential diagnosis of various liver diseases or may be of prognostic significance. Apparently, the determination of the free tyrosin in the blood filtrate can be of value in every one of these ways. However, minimal degrees of liver dysfunction can not be determined by this test. A tyrosin clearance test as suggested in this contribution may enhance the sensitivity of it.

### CONCLUSION

Free tyrosin in the blood filtrate does not appear in the fasting controls. In the non-fasting controls free tyrosin was demonstrated in less than 10 per cent of the cases studied. There probably is some mild liver damage in these cases. Tyrosinemia appears in more than 80 per cent of patients who have demonstrable diffuse liver damage. The incidence of positive findings in focal injury of the liver is much smaller. The demonstration of free tyrosin in the blood filtrate in the fasting state is with very few exceptions an indication of liver damage. On the other hand, the absence of tyrosin does not exclude liver disease.

### REFERENCES

1. Frierichs, F. T.: Offenes Schreiben an den Herrn Hofrath Dr. Oppolzer in Wien. *Wien Med. Wochenschrift*, 4:465, 1854.
2. Eppinger, H. and Winkler, P.: Die Krankheiten der Leber. Leipzig, Georg Thieme, 1926.
3. Lichtmann, S. S. and Sobotka, L.: An Enzymatic Method for the Detection and Estimation of Tyrosine in Urine. *J. Biol. Chem.*, 85:261, 1929.
4. Neuberg, C. and Richter, P. F.: Über das Vorkommen von Freien Aminosäuren (Leucin, Tyrosin, Lysin) im Blute bei Akuter Leberatrophy. *Deut. Med. Wochenschrift*, 30:499, 1904.
5. Jankelson, I. R., Segal, M. S. and Aisner, M.: Tyrosinemia and Its Relation to Pathology of the Liver. *Am. J. Med. Sci.*, 193:241 Feb., 1938.
6. Unpublished data.
7. Lichtmann, S. S.: Origin and Significance of Tyrosinuria in Diseases of the Liver. *Arch. Int. Med.*, 53:80, 1934.
8. Jankelson, I. R., Segal, M. S. and Aisner, M.: Tyrosinemia and Takata-Arn Tests in Cirrhosis of the Liver. *Review of Gastro-Ent.*, 6:341, July-Aug., 1939.

## A Study of the Excretion of Bromsulphthalein in the Bile\*

By

C. W. WIRTS, JR., M.D.†

and

A. CANTAROW, M.D.

PHILADELPHIA, PENNSYLVANIA

SINCE the introduction of the halogenated phthaleins into the clinical and experimental investigation of hepatic function (1, 2), a variety of methods have been proposed for estimating the capacity of the liver for eliminating these substances. Originally, the

quantity of dye (phenoltetrachlorphthalein) excreted in the feces was estimated (1, 3, 4, 5), but the obvious technical difficulties inherent in this procedure rendered the results of doubtful value. With the introduction of the modern procedure of duodenal intubation and biliary drainage attempts were made to evaluate the state of hepatic function by determining (a) the time of appearance of the dye in bile obtained

\*From the Department of Medicine and Physiology, Jefferson Medical College, and the Laboratory of Biochemistry, Jefferson Hospital.  
†Ross V. Patterson Fellow in Gastro-Enterology.  
Read at the Annual Meeting of the American Gastro-Enterological Association at Atlantic City, N. J., May 6, 1941.



by this means, and (b) the total quantity eliminated in the bile during varying periods of study (3, 6, 7, 8). However, the relative crudity of methods then available made accurate quantitative estimation of the dye virtually impossible. Since the introduction of the procedure of determining the degree of retention of the dye in the blood serum or plasma (9), all methods employed previously have been discarded.

The widespread use of this procedure in clinical and experimental studies of liver function has resulted in the accumulation of a large volume of valuable data, but there is still no exact knowledge of the mechanism of removal of bromsulphthalein from the body. Two facts appear to be definitely established: (a) following intravenous injection of 2 mg. per kilogram of body weight, the dye is removed from the blood very rapidly (85-95 per cent in 5 minutes and 100 per cent in 30 minutes); even in the presence of total bile stasis it disappears from the blood stream within 3 to

8 hours (10). (b) Excretion of the dye in the bile continues, under normal conditions, over a period of several hours. It appears, therefore, that there are two phases of the removal of this substance from the organism. There is some evidence (11, 12, 13) that the first, i.e., the rapid removal of the dye from the blood stream, is effected, in part at least, through the activity of the Kupffer and other reticuloendothelial cells. The second phase, i.e., the gradual elimination in the bile, probably depends largely upon the functional activity of the hepatic polygonal cells.

The present study constitutes an attempt to investigate further the mechanism of removal of bromsulphthalein from the body under normal and abnormal conditions.

#### MATERIAL AND METHODS

Studies were made upon three groups of subjects: (1) 28 ambulatory patients regarded as having

TABLE I  
*Bromsulphthalein excretion in subjects studied by duodenal intubation, showing no dye retention in blood*

| Normal Results       |                    |          |                                 |      |      |      |      |      |     |     |                |             |
|----------------------|--------------------|----------|---------------------------------|------|------|------|------|------|-----|-----|----------------|-------------|
| Case                 | Blood              |          | Milligrams Dye Per 100 cc. Bile |      |      |      |      |      |     |     | Total Excreted |             |
|                      | Bilirubin<br>mg. % | Dye<br>% | 15                              | 30   | 45   | 60   | 75   | 90   | 105 | 120 | 1 Hr.<br>%     | 2 Hrs.<br>% |
|                      |                    |          |                                 |      |      |      |      |      |     |     |                |             |
| 1                    |                    |          |                                 | 25   | 60   | 19   | 25   | 11   | 5   | 0   | 68             | 87          |
| 2                    |                    |          | 17                              | 30   | 23   | 52   | 15   | 2.5  | 12  | 7.5 | 61             | 74          |
| 3                    |                    | 0        | 0                               | 12   | 5    | 9    | 1    | 24   | 12  | 4   | 50             | 81          |
| 4                    |                    | 0        | 15                              | 55   | 162  | 125  | 70   | 40   | 30  | 25  | 73             | 100         |
|                      |                    | 0        | 1.5                             | 50   | 92   | 140  | 200  | 162  | 54  | 40  | 52             | 97          |
|                      |                    | 0        | 5                               | 67   | 70   | 15   | 67   | 53   | 32  | 16  | 54             | 46          |
| 5                    |                    | 0        | 0                               | 42   | 75   | 25   | 24   | 0    | 0   | 0   | 70             | 74          |
| 6                    |                    | 0        | 0.5                             | 1    | 7    | 154  | 29   | 32   | 9   | 9   | 40             | 67          |
| 7                    |                    | 0        | 2                               | 37   | 53   | 29   | 23   | 28   | 19  | 15  | 53             | 67          |
| 8                    | 0.2                | 0        | 1.5                             | 38   | 68   | 12   | 5    | 41   | 53  | 36  | 40             | 81          |
| 9                    | 0.2                | 0        | 0.5                             | 4.5  | 165  | 175  | 165  | 56   | 57  | 58  | 81             | 77          |
| 10                   | 0.2                | 0        | 8.5                             | 75   | 53   | 12   |      | 2    | 19  | 6   | 79             | 55          |
| Questionable Results |                    |          |                                 |      |      |      |      |      |     |     |                |             |
| 11                   |                    | 0        | 0                               | 27   | 75   | 65   | 20   | 25   | 22  | 17  | 45             | 50          |
| 12                   |                    | 0        | 0.5                             | 12   | 42   | 10   | 12   | 42   | 40  | 17  | 29             | 33          |
| 13                   | 0.5                | 0        | 19                              | 14   | 2    | 0    | >0   | 25   | 11  | 1   | 12             | 72          |
| 14                   |                    | 0        | 0                               | 1    | 10   | 102  | 57   | 47   | 42  | 36  | 19             | 45          |
| 15                   | 0.3                | 0        | 2                               | 2    | 63   | 52   | 15   | 13   | 16  | 3   | 31             | 77          |
| 16                   | 0.7                | 0        | 0                               | 28.5 | 68   | 40   | 0.0  | 65   | 5   | 8   | 15             | 72          |
| 17                   | 0.3                | 0        | 1                               | 67   | 55   | 65   | 30   | 24   | 5   | 5   | 31             | 41          |
| 18                   | 0.2                | 0        | 2                               | 62   | 101  | 18.5 | 24   | 14.5 | 26  | 9   | 24             | 33          |
|                      | 0.2                | 0        | 17.5                            | 8.5  | 28.5 | 23.5 | 11   | 3    | 14  | 5.5 | 25             | 34          |
| 19                   | 0.3                | 0        | 1.5                             | 18   | 18   | 43   | 29   | 23   | 27  | 17  | 71             | 47          |
| 20                   | 0.3                | 0        | 1                               | 26   | 167  | 78   | 1    | 42   | 34  | 75  | 23             | 87          |
| 21                   | 0.3                | 0        | 1.5                             | 13.5 | 22   | 37   | 28   | 31   | 36  | 0   | 14             | 27          |
| 22                   | 0.2                | 0        | 2                               | 2    | 63   | 58   | 17   | 13   | 10  | 9   | 27             | 33          |
| Abnormal Results     |                    |          |                                 |      |      |      |      |      |     |     |                |             |
| 23                   |                    | 0        | 4.5                             | 4.5  | 13   | 5.5  | 87   | 42   | 5   | 2.5 | 5              | 47          |
| 24                   |                    | 0        | 3                               | 37   | 17   | 11   | 22   | 29   | 12  | 9   | 34             | 54          |
| 25                   |                    | 0        | 8                               | 34   | 48   | 39   | 77   | 19   | 17  | 15  | 26             | 77          |
| 26                   | 8.2                | 0        | 1                               | 5    | 19   | 6    | 7    | 4    | 6   | 7   | 14             | 43          |
| 27                   | 0.7                | 0        | 0.5                             | 3    | 8    | 21.5 | 19.5 | 27.5 | 26  | 5   | 13             | 27          |
| 28                   | 6.2                | 0        | 0.5                             | 33   | 78   | 18   | 5.5  | 2.5  | 1.7 | 50  | 12             | 47          |

chronic biliary tract disease (31 determinations); (2) 15 cholecystectomized patients with T-tubes in the common bile duct (36 determinations); (3) 4 cholecystectomized, bile-fistula dogs with and without varying degrees of bile stasis and hepatocellular damage (40 determinations). In the first group, bile was collected by duodenal intubation by the usual method, with magnesium sulphate stimulation, in fifteen minute samples over a period of at least two hours. In many instances the use of the gastro-duodenal Diamond tube has facilitated collection of duodenal contents

uncontaminated by gastric juice. In the second and third groups, the bile was allowed to drain directly into test tubes and was collected in fifteen minute samples over periods of two to six hours. In groups 1 and 3 the volume of each specimen was measured accurately.

After a steady flow of bile was obtained bromsulphthalein was injected intravenously in a dosage of 2 mg. per kilogram of body weight and blood was withdrawn at the end of thirty minutes, for estimation of the degree of dye retention and the serum bilirubin

TABLE II

*Bromsulphthalein excretion in cholecystectomized subjects with T-tubes in the common bile duct*

| Case | Date  | Blood   |  | Milligrams Dye Per 100 cc. Bile                        |  |  |  |  |   |   |   |  |
|------|---|---|--|--|--|--|--|--|---|---|---|--|
|      |   | Bilirubin<br>mg. %  | Dye<br>%   | 15   | 30   | Minutes                                      |  |  |   |   |   |  |
|      |   |   |  |  |  | 45   | 60   | 75   | 90  | 105   | 120   |  |
| 1    | 1-27<br>2-5<br>2-21<br>2-28   | 16.4<br>8.0<br>8.0<br>9.8   | 80<br>80<br>80<br>80                                   | 2<br>10.5<br>1<br>2                                    | 1.5<br>7.5<br>2<br>4                               | 1<br>4.0<br>1                                | 3<br>10.5<br>5<br>2                              | 14<br>11<br>11<br>2  | 23<br>15<br>15<br>2                                     | 28<br>23<br>23<br>2                                     |   |  |
| 2    | 8-12<br>8-28<br>9-9   | 1.0<br>0.9<br>1.4   | 30<br>15<br>10   | 3.7<br>0<br>0  | 3.7<br>0<br>52                                     | 2.5<br>12<br>110                             | 2.5<br>37<br>135                                 | 2.5<br>110<br>135  | 2.5<br>150<br>125                                       | 42<br>155<br>125  | 167<br>250<br>105                                     | Duodenal drainage<br>1 hr. 18%; 2 hrs. 42%   |
| 3    | 9-24  | 1.0   | 10   | 9  | 9  | 105  | 145  | 190  | 195   | 177   | 182   |  |
| 4    | 10-3  | 0.4   | 0  | 10   | 92   | 260  | 290  | 369  | 310   | 260   | 242   |  |
| 5    | 10-8<br>10-11<br>10-14  | <br>0.9<br>0.9  | <br>0<br>10  | 2.5<br>0<br>1.3<br>2                                   | 4<br>0<br>2.5<br>3                                 | 4<br>2.5<br>2.5<br>3                         | 4<br>5<br>1.5<br>4                               | 5<br>9<br>2.5<br>3   | 9<br>11<br>7.5<br>8                                     | 15<br>19<br>16<br>18                                    | 21<br>45<br>41<br>27                                  |  |
| 6    | 10-9<br>10-11<br>10-14<br>10-19<br>10-28<br>11-4<br>11-7<br>11-11<br>11-14<br>11-18 | 27.4<br>24.4<br><br>13.9<br>10.7<br>13.5<br>11.8<br>8.6<br>8.2<br>5.6 | 80<br>50<br><br>60<br>40<br>10<br>40<br>35<br>30<br>15 | 0<br>0<br>0<br>0<br>3.5<br>1<br>0.5<br>3.5<br>1.5<br>2 | 0<br>0<br>0.6<br>0<br>3<br>3.5<br>1<br>4<br>1<br>2 | 4<br>1<br>0<br>3<br>10<br>4<br>9.5<br>7<br>2 | 1<br>4<br>18<br>6<br>25<br>9.5<br>15<br>20<br>10 | 5<br>7.5<br>10.5<br>22<br>34<br>35<br>15<br>25<br>30<br>34 | 7<br>7.5<br>8<br>20<br>42<br>31<br>32<br>20<br>32<br>41 | 7<br>7.5<br>0<br>20<br>40<br>32<br>19<br>27<br>27<br>45 | 7<br>9<br>8<br>19<br>30<br>35<br>19<br>29<br>21<br>64 |  |
| 7    | 11-4<br>11-9  | 0.2<br>0.5  | 0<br>0   | 1<br>1   | 11<br>6  | 63<br>49                                     | 92<br>84   | 130<br>72  | 148<br>63   | 142<br>62   | 132<br>61   |  |
| 8    | 12-19<br>12-23<br>1-27<br><br>2-10  | 0.9<br>0.9<br><br>0.2   | 10<br>0<br><br>0                                       | 0<br>1<br>2  | 21<br>2<br>37                                      | 113<br>50<br>53                              | 136<br>126<br>29                                 | 100<br>165<br>23   | 63<br>183<br>28   | 84<br>198<br>19   | 88<br>204<br>19                                       | Duodenal drainage<br>1 hr. 53%; 2 hrs. 87%<br><br>Duodenal drainage<br>1 hr. 12%; 2 hrs. 37% |
| 9    | 11-26<br>12-2   | 1.6<br>1.9  | 40<br>15   | 1<br>0.5   | 1<br>3   | 6<br>53                                      | 18<br>57   | 27<br>51   | 32<br>63  | 33<br>61  | 30<br>52  |  |
| 10   | 12-6  | 0.4   | 0  | 0  | 1  | 5  | 40   | 96   | 110   | 148   | 178   |  |
| 11   | 4-13<br>4-30  | 13.1<br>7.3   | 80<br>40   | 0.5<br>0   | 0.5<br>0.5   | 0.1<br>0                                     | 0.1<br>0   | 1.5<br>0.5   | 1.0<br>2.0  | 1.5<br>2.5  | 2.0<br>7.5  |  |
| 12   | 4-8<br>4-14   | 0.9<br>0.5  | 10<br>15   | 1<br>0.5   | 2.5<br>0.5   | 37<br>6                                      | 74<br>86.5                                       | 177<br>147   | 152<br>158  | 136<br>200  | 120<br>183  |  |
| 13   | 4-22  | 0.7   | 0  | 2  | 2  | 44   | 90   | 170  | 164   | 155   | 152   |  |
| 14   | 4-22  | 18.8  | 65   | 4.5  | 7.5  | 12.5   | 19   | 21   | 23.5  | 28.5  | 23  |  |
| 15   | 4-30  | 0.6   | 0  | 0.5  | 13.5   | 95   | 100  | 164  | 94  | —   | 118   |  |

concentration. The concentration of bromsulphthalein in the bile was determined by a method described elsewhere (15), employing 0.1 cc. of bile, the final color reading being made with the Evelyn photoelectric colorimeter (14). The data obtained included (a) the retention of dye in the blood at the end of thirty minutes, (b) the serum bilirubin concentration, (c) the concentration of dye in each fifteen-minute

(2) delayed attainment of maximum concentration; (3) prolonged high curve of excretion; (4) subnormal concentration (flat type of curve); (5) abnormally low total excretion in one or two hour periods after injection.

### COMMENT

Analysis of these data reveals several points of interest. The observation is confirmed that, whereas bromsulphthalein leaves the blood stream very rapidly under normal conditions, its elimination in the bile continues over a period of several hours. The time relationships of these two phenomena are indicated schematically in Fig. 1. As was stated previously, this suggests that two separate or related mechanisms are involved in the removal of the dye from the body, and there is some evidence the first (rapid removal from the blood) is related to reticuloendothelial cell activity, perhaps largely to that of the Kupffer cells (11, 12, 13). Studies bearing upon this problem are now in progress and will be reported upon elsewhere; findings obtained to date tend to support this hypothesis. There seems to be little doubt that the more gradual process of excretion of the dye in the bile is a function of the polygonal cells of the liver. It would appear, therefore, that simultaneous investigation of the rate of removal of bromsulphthalein from the blood and of the manner of its elimination in the bile, by the method outlined here, affords a means of studying these two phases of the mechanism whereby the dye is removed from the organism.

Certain of the data indicate clearly that each of

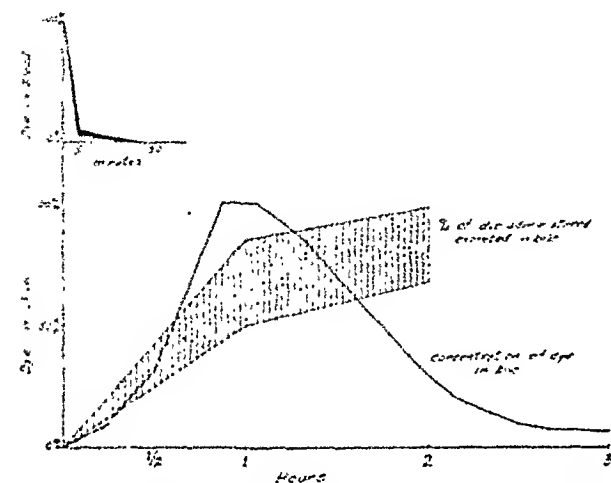


Fig. 1. Schematic representation of time relationships of removal of bromsulphthalein from the blood and excretion in the bile.

sample of bile and (d) the total quantity of dye eliminated in the bile within one and two hours after its administration.

### RESULTS

The data are presented in detail in Tables I-III. Values were regarded as normal when all of the following criteria were fulfilled: (1) normal serum bilirubin concentration; (2) no dye remaining in blood at the end of thirty minutes; (3) no other demonstrable abnormality of liver function; (4) a curve of dye concentration in the bile which rose to a maximum and fell to a comparatively low level at the end of two hours; (5) the elimination of a large proportion of the quantity of dye administered within the two-hour period. When selected on this basis normal excretion of bromsulphthalein in the bile presented the following features (Fig. 1): (1) the dye appeared in the bile usually, but not invariably, during the first fifteen minutes; (2) it attained a maximum concentration in forty-five to seventy-five minutes, falling subsequently to a relatively low level at two hours but often not disappearing completely for five to six hours; (3) 50-83 per cent of the quantity injected was excreted in the first hour and 67-100 per cent in the first two hours. In the presence of normal excretion values, the maximum concentration observed in human subjects ranged from 24 to 200 mg. per 100 cc. and in dogs 42 to 252 mg. per 100 cc. The maximum concentrations observed in the entire series of subjects were as follows: (a) duodenal drainage material, 200 mg. per 100 cc.; (b) human common-duct bile, 259 mg. per 100 cc.; (c) dog common-duct bile, 532 mg. per 100 cc.

Abnormal excretion of bromsulphthalein in the bile was evidenced by one or more of the following phenomena: (1) delayed appearance of the dye in the bile;

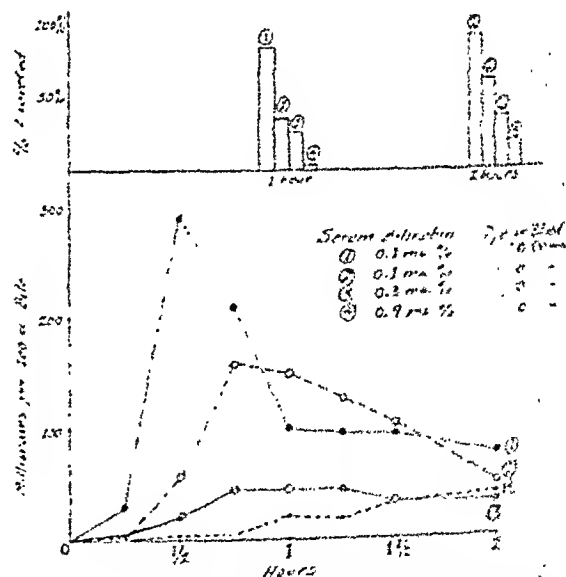


Fig. 2. Increasing abnormality of bromsulphthalein excretion with no retention in blood during period of progressive obstruction of common bile duct in dogs.

these two phases may be affected independently of the other. In Table I are presented findings obtained in subjects with no abnormal retention of dye in the blood, i.e., a normal first phase (normal Kupffer cell activity?), but with abnormal excretion of the dye in the bile (abnormal polygonal cell function?). Similar instances occur in Table II (Cases 4, 5, 7, 8, 10, 11, 15) and Table III. In the case of observations in

TABLE III  
*Bromsulphthalein excretion in cholecystectomized bile-fistula dogs*

| Dog | Date     | Blood              |          | Minutes   |     |     |     |     |     |     |     | Total Excretion |             |
|-----|----------|--------------------|----------|-----------|-----|-----|-----|-----|-----|-----|-----|-----------------|-------------|
|     |          | Bilirubin<br>mg. % | Dye<br>% | 15        | 30  | 45  | 60  | 75  | 90  | 105 | 120 | 1 Hr.<br>%      | 2 Hrs.<br>% |
|     |          |                    |          |           |     |     |     |     |     |     |     |                 |             |
| 1   | 2-8-41   |                    |          | Operation |     |     |     |     |     |     |     |                 |             |
|     | 2-18-41  | 2.4                | 50       | 1         | 1   | 4   | 27  | 48  | 54  | 61  | 51  | 1.3             | 7.7         |
|     | 2-18-41  | 1                  | 15       | 1         | 3   | 26  | 49  | 31  | 19  | 19  | 18  | 6.3             | 11.2        |
|     | 2-20-41  | 0.7                | 10       | 4         | 32  | 30  | 26  | 19  | 19  | 20  | 19  | 7.6             | 32.9        |
|     | 2-23-41  | 0.4                | 10       | 7         | 53  | 75  | 146 | 90  | 178 | 160 | 108 | 18.2            | 51.9        |
|     | 2-28-41  | 0.2                | 20       | 22        | 51  | 28  | 16  | 9   | 7   | 4   | 3   | 30.4            | 34          |
|     | 3-4-41   | 0.7                | 10       | 1         | 13  | 42  | 55  | 55  | 44  | 36  | 30  | 8.4             | 20.4        |
|     | 3-6-41   | 0.3                | 0        | 40        | 76  | 45  | 24  | 14  | 12  | 12  | 10  | 71.9            | 81.3*       |
|     | 3-11-41  | 0.3                | 0        | 17        | 75  | 48  | 30  | 22  | 16  | 12  | 10  | 52.4            | 65.1*       |
|     | 3-13-41  | 0.3                | 20       | 3         | 11  | 10  | 8   | 8   | 8   | 11  | 9   | 12.3            | 18.9†       |
|     | 3-14-41  | 0.05               | 0        | 3         | 30  | 132 | 134 | 110 | 97  | 76  | 52  | 23.1            | 47.2        |
|     | 3-18-41  | 0.3                | 15       | 1         | 16  | 37  | 47  | 47  | 47  | 40  | 42  | 14.1            | 33.5†       |
|     | 3-20-41  | 0.06               | 10       | 1         | 22  | 54  | 92  | 108 | 86  | 98  | 86  | 9.3             | 31.8        |
|     | 3-21-41  | 0.1                | 0        | 12        | 111 | 110 | 88  | 59  | 39  | 29  | 25  | 54.7            | 71.5        |
| 2   | 2-13-41  |                    |          | Operation |     |     |     |     |     |     |     |                 |             |
|     | 2-18-41  | 0.3                | 0        | 0         | 29  | 128 | 132 | 106 | 70  | 46  | 46  | 27.6            | 47.6        |
|     | 2-20-41  | 0.5                | 0        | 1         | 17  | 132 | 249 | 210 | 130 | 77  | 51  | 25.7            | 55.1        |
|     | 2-25-41  | 0.1                | 0        | 2         | 27  | 198 | 285 | 219 | 165 | 120 | 85  | 20.4            | 47.6        |
|     | 2-28-41  | 0.4                | 20       | 1         | 20  | 41  | 37  | 27  | 16  | 14  | 9   | 32.7            | 54.1*       |
|     | 3-6-41   | 0.1                | 0        | 2         | 24  | 44  | 52  | 34  | 28  | 26  | 20  | 41.1            | 56.8*       |
| 3   | 10-10-40 |                    |          | Operation |     |     |     |     |     |     |     |                 |             |
|     | 10-15-40 | 0.2                | 0        | 0         | 2   | 375 | 532 | 427 | 367 | 200 | 130 | 36              | 83          |
|     | 10-21-40 | 0.2                | 0        | 0         | 105 | 337 | 307 | 405 | 427 | 367 | 307 | 59              | 72          |
|     | 10-23-40 | 0.1                | 0        | 29        | 292 | 210 | 100 | 97  | 95  | 95  | 77  | 83              | 91          |
|     | 10-26-40 |                    |          | 5         | 152 | 375 | 300 | 235 | 175 |     | 110 | 70              | 85          |
|     | 11-1-40  | 0.2                | 10       | 1         | 120 | 307 | 240 | 175 |     | 145 | 112 | 65              | 88          |
|     | 11-2-40  | 0.4                | 10       | 7         | 145 | 282 | 217 | 123 | 86  | 90  | 75  | 52              | 70          |
|     | 11-3-40  |                    |          | 5         | 7   | 26  | 62  | 80  | 120 | 122 | 177 | 3.7             | 19          |
|     | 11-6-40  | 0.1                | 0        | 1         | 59  | 159 | 150 | 127 | 111 | 76  | 55  | 35              | 61          |
|     | 11-9-40  | 0.2                |          | 1         | 6   | 22  | 29  | 25  | 20  | 18  | 15  | 7.4             | 14          |
|     | 11-12-40 | 0.3                | 0        | 2         | 19  | 46  | 45  | 45  | 33  | 25  | 30  | 26              | 36          |
|     | 11-19-40 | 0.8                | 20       | 1         | 1   | 8   | 23  | 39  | 45  | 35  | 33  | 1.6             | 10.6        |
|     | 11-26-40 | 0.7                | 10       | 1         | 0   | 1   | 22  | 26  | 38  | 33  | 34  | 2.1             | 8.1         |
| 4   | 8-9-40   |                    |          | Operation |     |     |     |     |     |     |     |                 |             |
|     | 8-13-40  | 1.7                | 40       | 4         | 60  | 100 | 60  | 25  | 20  | 30  | 20  | 16              | 25.6        |
|     | 8-15-40  | 3.1                | 50       | 1         | 10  | 12  | 14  | 20  | 10  | 10  | 12  | 6.2             | 11.5        |
|     | 8-17-40  | 2.3                | 40       | 10        | 48  | 55  | 45  | 32  | 30  | 30  | 33  | 4.9             | 12.2        |
|     | 8-19-40  | 1.7                | 20       | 4         | 25  | 67  | 35  | 35  | 27  | 27  | 27  | 15.8            | 21.6        |
|     | 9-3-40   | 2.3                | 20       | 1         | 2   | 15  | 7   | 7   | 6   | 7   | 9   | 6.6             | 9.9         |
|     | 9-9-40   | 0.4                | 0        | 0         | 25  | 110 | 225 | 162 | 157 | 137 | 125 | 39.6            | 74.5        |
|     | 9-12-40  | 0.08               | 0        | 1         | 1   | 31  | 42  | 31  | 18  | 15  | 9   | 57.1            | 76.5        |
|     | 9-18-40  | 0.04               | 0        | 62        | 240 | 185 | 105 | 62  | 33  | 22  | 15  | 73.5            | 87.3        |
|     | 9-21-40  |                    |          | 0         | 80  | 140 | 102 | 52  | 30  | 22  | 15  | 81              | 98.2        |

\*150-200 cc. bile run into duodenum just before test.  
†20 cc. 20% India Ink intravenously 1½ hour before test.

upon material obtained by duodenal intubation, if the curve of dye excretion appears to be normal, a somewhat subnormal total recovery may be due to failure to obtain all of the bile in the drainage material. In our experience, this does not occur frequently but, in evaluating the findings, both the character of the curve and the total recovery must be taken into consideration. A striking example of the dissociation of the two phases of this mechanism is illustrated in Fig. 2. These data were obtained in consecutive studies in a bile-fistula dog during a period of progressively increasing bile stasis. Curve 1 is essentially normal, as is the total dye excretion at that time. Curves 2, 3 and 4 became progressively abnormal with corresponding progressive decrease in the total dye excretion. At no time was there abnormal retention of dye in the blood. These findings suggest that during the early period of bile stasis the obstruction to the flow of bile may interfere with the excretion of the dye by the hepatic cells for a considerable period of time before the capacity of the liver (Kupffer cells?) for removing the dye from the blood is impaired.

The ease with which this procedure may be carried out and the accuracy with which the concentration of

the dye in the bile may be determined render the method of study readily available clinically. The preliminary observations suggest that data obtained in this manner may prove to be of considerable value in detecting abnormalities of bromsulphthalein excretion in the absence of abnormal retention of the dye in the blood.

### SUMMARY

A procedure is described whereby the curve of elimination of bromsulphthalein in the bile is determined simultaneously with the estimation of the degree of its retention in the blood. Studies were performed upon human subjects and bile-fistula dogs. The data obtained support the hypothesis that a dual mechanism is involved in the removal of bromsulphthalein from the organism. The first phase, i.e., its rapid removal from the blood stream, may possibly be largely a function of the Kupffer cell activity, while the second phase, i.e., its gradual excretion in the bile, is probably a function of hepatic polygonal cell activity. Instances are presented of apparent dissociation of these two phases of the dye excretion mechanism, which may be detected readily by means of this procedure.

### REFERENCES

1. Rowntree, L. G., Hurwitz, S. H. and Bloomfield, A. L.: An Experimental and Clinical Study of the Value of Phenotetrachlorophthalein as a Test for Hepatic Function. *Bull. Johns Hopkins Hosp.*, 24:327, 1913.
2. Whipple, G. H., Peichthal, T. C. and Clark, A. H.: Tests for Hepatic Function and Disease Under Experimental Conditions—Phenotetrachlorophthalein. *Bull. Johns Hopkins Hosp.*, 24:343, 1913.
3. Kahn, M. and Johnston, J. B.: The Phenotetrachlorophthalein Test for Liver Function. *New York Med. J.*, 102:448, 1913.
4. Krambhaar, E. B.: Present Status of Functional Liver Tests. *New York Med. J.*, 100:719, 1914.
5. Sisson, W. H.: A Clinical Study of Two Hepatic Functional Tests. *Arch. Int. Med.*, 11:404, 1914.
6. McNeill, H. L.: The Quantitative Estimation of Phenotetrachlorophthalein Excreted in the Fresh Bile in Disease of the Liver. *J. Lab. and Clin. Med.*, 1:822, 1915.
7. Aaron, A. H., Beck, E. C. and Schneider, H. C.: The Phenotetrachlorophthalein Test for Liver Function. *J. A. M. A.*, 71:1631, 1921.
8. Nicard, G. M. and Backus, H. L.: Observations on the Value of Phenotetrachlorophthalein in Estimating Liver Function. *Arch. Int. Med.*, 31:522, 1923.
9. Rosenthal, S. M.: A New Method of Testing Liver Function with Phenotetrachlorophthalein. *J. A. M. A.*, 2151:79, 1922.
10. Rosenthal, S. M. and White, E. C.: Studies in Hepatic Function. *J. Pharm. and Exper. Therap.*, 24:255, 1924.
11. Rosenthal, S. M. and White, E. C.: Clinical Application of the Bromsulphthalein Test for Hepatic Function. *J. A. M. A.*, 54:1112, 1925.
12. Snell, A. M., Greene, C. H. and Rowntree, L. G.: Diseases of the Liver. II. A Comparative Study of Certain Tests for Hepatic Function in Experimental Obstructive Jaundice. *Arch. Int. Med.*, 36:272, 1925.
13. Mills, M. A. and Dravstedt, C. A.: Bromsulphthalein as a Retention Test as a Measure of Functional Activity of Reticuloendothelial System. *Proc. Soc. Exper. Biol. and Med.*, 24:229, 1925.
14. Mills, M. A. and Dravstedt, C. A.: Removal of Intravenously Injected Bromsulphthalein from the Blood Stream of the Dog. *Arch. Int. Med.*, 12:215, 1928.
15. Klein, R. I. and Levinson, S. A.: Removal of Bromsulphthalein from the Blood Stream by the Reticuloendothelial System. *Proc. Soc. Exper. Biol. and Med.*, 31:179, 1933.
16. Malloy, H. T. and Evelyn, K. A.: The Determination of Bile with the Photoelectric Colorimeter. *J. Biol. Chem.*, 109:131, 1937.
17. Cantarow, A. and Wirtz, C. W., Jr.: Studies of the Excretion of Bromsulphthalein in the Bile. *Proc. Soc. Exper. Biol. and Med.*, 47:242, 1941.

## Limitations in the Use of Color Indicators in Gastric Analysis<sup>1</sup>

By

J. EDWARD BERK, M.D., M.Sc. (Med.)<sup>2</sup> J. EARL THOMAS, M.D.

and

MARTIN E. REHFUSS, M.D.

PHILADELPHIA, PENNSYLVANIA

IN the standardized procedures of gastric analysis as now almost universally applied, the acidity of the gastric contents is determined titrimetrically with the use of color indicators. Dimethylaminoazobenzene (Teopfer's reagent) and phenolphthalein are generally used despite the objections which have been made

to them (4, 6, 7, 8, 9, 14). In the course of some current investigations on the reaction of the gastric and duodenal contents, an opportunity was afforded to further evaluate their reliability. It is our purpose in this communication to report some limitations which we observed in the use of the indicators mentioned that might influence their employment in routine clinical practice.

### MATERIAL

Gastric and duodenal contents were collected by means of special tubes from 7 dogs and 25 humans, both before and after the feeding of an Eagle-Bro-

<sup>1</sup>From the Departments of Physiology and Medicine of The Jefferson Medical College.  
<sup>2</sup>Added by a Grant from John Wirth & Partner, Inc., 1300 N. 17th Street, Philadelphia, to Gastro-Enterology.  
One of the papers submitted by Dr. Berk to the Faculty of the Graduate School of Medicine of the University of Pennsylvania in partial fulfillment of the requirements for the degree of Doctor of Medical Science (M.Sc. (Med.)) for graduate work in internal medicine.  
Published June 12, 1942.

consisting of 2 pieces of stale bread or toast and 250 cc. of water. Approximately 1500 measurements of free acid and an equal number of estimations of total acidity were made. Additional estimations totaling approximately 800 were made on the duodenal specimens for what was called the excess neutralizing ability. This consisted of the amount of N/10 hydrochloric acid required to cause a positive reaction for free acid. All observations upon which the present report is based were made by one person. For the determination of free acid and the duodenal neutralizing ability Töepfer's reagent was used, an orange-yellow color being taken as the end point. For the determination of total acidity phenolphthalein was used, a persistent reddish-pink being taken as the end point. In addition, the pH was determined on each unfiltered and undiluted specimen by means of a Leeds-Northrup pH indicator which uses a glass electrode.

#### *The Reliability of the End Point*

In the course of the preceding study, specimens were chosen at random on different days immediately after the titrations on each had been completed. The pH at the end point chosen was then determined electrometrically without delay.

As representative of the pH at the Töepfer reagent end point, 25 gastric post-meal samples on which free

TABLE I

*The pH at the titrimetric end points of Töepfer's reagent and phenolphthalein in randomly selected post-meal samples of gastric and duodenal contents*

|                    | Töepfer's Reagent<br>(50 Samples) | Phenolphthalein<br>(50 Samples) |
|--------------------|-----------------------------------|---------------------------------|
| Average            | 3.36                              | 9.07                            |
| Standard deviation | ± 0.18                            | ± 0.26                          |
| Range              | 2.88-3.72                         | 8.52-9.57                       |

acid had been measured and 25 duodenal post-meal samples on which neutralizing ability had been estimated were selected at random. The average of the two groups combined was pH 3.36 with a standard deviation of ± 0.18 and a range of 2.88 to 3.72 (Table I).

As representative of the pH at the phenolphthalein end point, 25 gastric and 25 duodenal post-meal samples on which total acidity had been determined were selected at random. The average of these two groups combined was pH 9.07 with a standard deviation of ± 0.26 and a range of 8.52 to 9.57 (Table I).

The extremes of pH at the end points of both indicators were well within the accepted ranges for each. It was startling, however, to find that the same observer doing repeated readings of supposedly the same color end point and relying upon color memory alone might vary as much as a full pH unit. This was impressed even more when, after statistical analysis, it was made clear that there was very little concentration of the readings around the mean pH and that more than 95 per cent of all future estimations made under the same conditions could be expected to fall in a similar wide pH range. Such deviations are much in excess of what might be expected (3, 9, 13).

In order to express the same error in clinical terms,

TABLE II

*The value in terms of clinical units of titratable free acid corresponding to the range in pH observed at the titrimetric end point of Töepfer's reagent*

| pH Range<br>(25 Samples)          | Average Corresponding<br>Range in Clinical Units |
|-----------------------------------|--|
| 2.8 to 2.9                        | 2.92   |
| 2.9 to 3.0                        | 3.56   |
| 3.0 to 3.1                        | 3.28   |
| 3.1 to 3.2                        | 3.20   |
| 3.2 to 3.3                        | 3.24   |
| 3.3 to 3.4                        | 2.88   |
| 3.4 to 3.5                        | 2.84   |
| 3.5 to 3.6                        | 2.68   |
| 3.6 to 3.7                        | 2.48   |
| 3.7 to 3.8                        | 2.40   |
| Total range studied<br>2.8 to 3.8 | This range corresponds to 29.5 clinical units    |

a comparative study was made of the pH range and its equivalent in units of titratable acidity. For this purpose accurate electrometric titrations were made using the same pH indicator. Fifty gastric and duodenal specimens were selected of which 7 were fasting samples and 43 were samples taken at various intervals after the ingestion of the Ewald meal. They were restricted choices only in that their initial pH corresponded with the lowest pH in the ranges being investigated. On half the samples titrations were made through the pH end point range of Töepfer's reagent (Table II). On the other half of the samples similar readings were made through the pH end point range of phenolphthalein (Table III).

Despite the fact that the end point pH range of both dimethylaminoazobenzene and phenolphthalein were approximately the same (one pH unit), the

TABLE III

*The value in terms of clinical units of titratable total acidity corresponding to the range in pH observed at the titrimetric end point of phenolphthalein*

| pH Range<br>(25 Samples)          | Average Corresponding<br>Range in Clinical Units |
|-----------------------------------|--|
| 8.5 to 8.6                        | 1.12   |
| 8.6 to 8.7                        | 1.10   |
| 8.7 to 8.8                        | 1.04   |
| 8.8 to 8.9                        | 1.02   |
| 8.9 to 9.0                        | 0.98   |
| 9.0 to 9.1                        | 1.00   |
| 9.1 to 9.2                        | 1.12   |
| 9.2 to 9.3                        | 1.12   |
| 9.3 to 9.4                        | 1.16   |
| 9.4 to 9.5                        | 1.20   |
| 9.5 to 9.6                        | 1.28   |
| Total range studied<br>8.5 to 9.6 | This range corresponds to 12.1 clinical units    |



equivalent value in titratable acidity with phenolphthalein was less than half that with dimethylaminoazobenzene. The important fact, however, is that a single observer making repeated readings of gastric and duodenal acidity with Töepfer's reagent from color memory alone is liable to an error from reading to reading as great as 30 units of titratable free acid. The same observer, making similar readings with phenolphthalein, is liable to an error from reading to reading as great as 12 units of titratable total acidity.

#### *The Effect of Dilution*

Knowing the range and the average pH at our end point with Töepfer's reagent, it became apparent that we were encountering a surprising number of false negative free acid readings. In the dogs alone, for example, out of 410 estimations of duodenal free acid, only 11 were positive to Töepfer's reagent yet the pH in 77 of the unfiltered, undiluted samples was 3.5 or below. It seemed that either something in the duodenal contents affected the color indicator or some change occurred during filtration and dilution.

There is no agreement in the standard laboratory texts on the method of preparation of samples for acidity titration (1, 2, 5, 6, 11, 14, 15, 16). We have

TABLE IV

*The effect of dilution (1:10) on the pH and the titratable acidity of 50 specially selected post-meal samples of gastric and duodenal contents. (Initial pH undiluted 2.1 to 2.9)*

|               | Average Difference Between<br>Undiluted and Diluted Samples |
|---------------|---|
| pH            | + 0.69  |
| Free Acid     | - 4.5   |
| Total Acidity | + 1.7   |

Undiluted samples positive for free acid 50 (100%).  
Diluted samples positive for free acid 21 (42%).

followed the method advocated by Rehfuess (14) and by Hawk and Bergeim (6), in which to 1 cc. of strained contents 10 cc. of distilled water is added and titration carried out with N 100 sodium hydroxide. It is generally conceded that the hydrogen ion concentration of a buffer solution will not be seriously altered by a moderate degree of dilution (3, 6). The gastric and duodenal contents are undoubtedly buffered to some degree and correspondingly little change of hydrogen ion concentration would be expected in them as a result of dilution. Yet Kahn and Stokes (10), using stomach contents, and Hollander (8), using pouch juice, were able to demonstrate a reduction in hydrogen ion concentration after dilution. Several observers (10, 12, 17, 18), moreover, have pointed out that a reduction in acidity may occur after simple filtration.

Fifty gastric and duodenal post-meal specimens were selected at random. On each the pH was determined both on the unfiltered, undiluted sample and again on the sample containing 1 cc. of strained contents plus 10 cc. of distilled water. We found that dilution did elevate the pH. As would be expected (3, 6, 10), the increase in pH was greatest when the original hydrogen ion concentration was greatest and

it progressively decreased as the original hydrogen ion concentration decreased.

On each of the 50 specimens, in addition, comparative titrations were made for free and total acidity on both diluted and undiluted samples. The differences for the entire group were not very striking. They appeared to be within the bounds of experimental error. In a few specimens, however, in which dilution had elevated the pH to close to the average of our end point with Töepfer's reagent (pH 3.3) the comparative titration values on the diluted and undiluted samples seemed significantly different. In order to evaluate the suggestion offered by this observation, further studies were undertaken.

The average increase in pH effected by dilution was 0.61 pH unit. Fifty additional gastric and duodenal post-meal specimens were selected whose pH in the unfiltered, undiluted samples was such that dilution might be expected to bring it close to our end point with Töepfer's reagent. In this group the average indicated free acid was 4.5 clinical units greater in the undiluted than in the diluted samples. There were 16 instances in the 50 (32 per cent) in which the reaction for free acid was negative in the diluted but positive in the undiluted samples (Table IV).

#### COMMENT

The distinctive advantages in the use of color indicators in gastric analysis are the ease and the rapidity with which the approximate hydrogen ion concentration may be measured. It is generally accepted that a very good approximation may be made, particularly by the same observer whose color memory is sharpened by the experience of many readings. The experimental error, however, in judging color is not inconsiderable. There are, furthermore, numerous additional errors which are inherent in the indicator method (3, 9, 13). Our experience indicates that a single observer with sufficient experience to render his readings supposedly standard is liable to a wide range of error in end point. The use of comparative colorimetric standards to control the end point, as advocated particularly by Hollander (8, 9), would probably increase the precision of the determination and reduce this error. The opportunity afforded to check our colorimetric end point by electrometric determination of the pH has undoubtedly improved the precision with which our end point readings are now made. Colorimetric standards are not generally used in routine clinical practice, however, and a means of electrometrically checking the colorimetric end point is ordinarily not available, so a considerable variation in acidity values is to be expected from this source alone.

In clinical practice there is great variability in the methods of preparing a sample for acidity titration. From our experience it seems of little consequence whether or not the sample is diluted except in those borderline cases where the hydrogen ion concentration is such that dilution may elevate the pH toward the Töepfer's reagent end point. In such cases false negative free acid readings may be obtained. It is possible, therefore, that in some instances there may be free acid in the gastric or duodenal contents which will be masked by dilution. When only single estimations are made or when only a few fractional estimations are

made at wide intervals, some patients may be incorrectly considered to be achlorhydric. It appears desirable, therefore, that in all borderline cases of achlorhydria or marked subacidity the titrations be repeated on undiluted samples.

### CONCLUSIONS AND SUMMARY

1. The end points of the color indicators dimethyl-aminoazobenzene (Töepfer's reagent) and phenolphthalein are uncertain. Even a single observer making repeated observations of a selected color end point from color memory alone is liable to a range of error of approximately a full pH unit. With dimethyl-aminoazobenzene this range of error expressed in equivalent clinical values may be as great as 30 clinical units of titratable free acid. With phenol-

phthalein it may be as great as 12 clinical units of titratable total acidity.

2. The use of comparative buffered colorimetric standards to control the end point should be considered as one means of reducing this error.

3. Generally the values of titratable acidity are little affected by the usual dilution of the sample. In some instances, however, where the color reaction with Töepfer's reagent in the diluted sample is negative for free acid or where the titratable free acid is very low, it is possible for the readings to be erroneous due to the dilution.

4. It is recommended that in all cases where there is negative or very low free acid, particularly if the number of samples examined is small, that the reactions be retested on undiluted samples.

### REFERENCES

1. Bodansky, M.: "Introduction to Physiological Chemistry." John Wiley and Sons, Inc., New York, 1938 (4th Edition).
2. Cantarow, A. and Trumper, M.: "Clinical Biochemistry." W. B. Saunders Co., Philadelphia, 1939 (2nd Edition).
3. Clark, W. M.: "The Determination of Hydrogen Ions." The Williams and Wilkins Co., Baltimore, 1928 (3rd Edition).
4. Collins, D. C.: A More Accurate Indicator in Determining the Total Acidity in Quantitative Gastric Analyses. *Med. Rec.*, 144:183, 1936.
5. Gradwohl, R. B. H.: "Clinical Laboratory Methods and Diagnosis." C. V. Mosby Co., St. Louis, 1933 (2nd Edition).
6. Hawk, P. B. and Bergeim, O.: "Practical Physiological Chemistry." P. Blakiston's Sons and Co., Philadelphia, 1937 (11th Edition).
7. Helmer, O. M. and Fouts, P. J.: Gastric Analysis Methods. *Am. J. Clin. Path.*, Technical Supplement, 7:41, 1937.
8. Hollander, F.: Studies in Gastric Secretion. II. A Comparison of Criteria of Acidity Used in This Investigation. *J. Biol. Chem.*, 91:451, 1931.
9. Hollander, F. and Penner, A.: History and Development of Gastric Analysis Procedure. *Am. J. Dig. Dis.*, 5:786, 1939.
10. Kahn, G. and Stokes, J., Jr.: The Comparison of the Electrometric and Colorimetric Methods for Determination of the pH of Gastric Contents. *J. Biol. Chem.*, 69:75, 1926.
11. Kolmer, J. A. and Boerner, F.: "Approved Laboratory Technique." D. Appleton-Century Co., New York, 1938 (2nd Edition).
12. Neeches, H.: Detection of Free Acid in Patients with Suspected Anacidity. *J. A. M. A.*, 103:106, 1934.
13. Rehberg, P. B.: XLI. A Method of Microtitration. *Biochem. J.*, 19:270, 1925.
14. Relbuss, M. E.: "Diagnosis and Treatment of Diseases of the Stomach." W. B. Saunders Co., Philadelphia, 1927.
15. Simmons, J. S. and Geatzkow, C. J.: "Laboratory Methods of the United States Army." Lea and Febiger, Philadelphia, 1935.
16. Todd, J. C. and Sanford, A. H.: "Clinical Diagnosis by Laboratory Methods." W. B. Saunders Co., Philadelphia, 1939 (9th Edition).
17. Pfundler, M.: Ueber eine neue Methode zur klinischen Functionsprüfung des Magens und deren physiologische Ergebnisse. *Deutsch. Arch. f. Klin. Med.*, 65:255, 1899.
18. Vos, H.: Het Bepalen Van Den Werkelijken Zuurgraad En Van De Geheele Hoeveelheid Zuur in Maaginhoud. *Nederland Tijdschr. Geneeskunde*, 66 (II) 2361, 1922, cited by Hollander, F. and Penner, A.: History and Development of Gastric Analysis Procedure. *Am. J. Dig. Dis.*, 5:789, 1939.

## The Excretion of Neutral Red by the Gastric Mucosa as Visualized Gastrosopically

By

HENRY H. LERNER, M.D., LEONARD ASHER, M.D.

and

KATHERINE ANDREWS, M.D.

BOSTON, MASSACHUSETTS

AMONG the many methods for studying the secretory activity of the gastric mucosa, the use of dyes has been included. Ever since Fuld (1) in 1908 showed that the stomach will excrete Azine dyes, workers have attempted to elaborate this approach.

The dye which held the greatest promise was aminodimethyl tolu aminozone hydrochloride known as "neutral red." This is an azine dye, a diamino derivative which forms red-mono-acid salts from weak bases. Its pH range is from 6.5 to 8 with a color change from red to yellow.

Fuld (1) demonstrated in Pavlov pouch dogs, that if neutral red were introduced into the stomach proper by a tube it would also appear in the pouch within a few minutes.

Finkelstein (2) in 1923 injected neutral red subcutaneously and noted that it appeared in both the Pavlov pouch as well as the stomach of the animal.

The first clinical application was made by Glaessner and Wittgenstein (3) in 1923 when (in 40 humans) they attempted to correlate the appearance time of dye in the gastric juice with the degree of acidity. From this work they drew the conclusion that the degree of acidity and the appearance time were related in that the greater the acidity the earlier the appearance of the dye. From this they reasoned that the acid secreting cells were responsible for the appearance of the dye.

This theory was disproved by Hirabayashi (4) in 1924 who showed that the excretory mechanism was of another nature, since the dye was present even if the secretion of hydrochloric acid was suppressed by silver nitrate.

Piersol (5) in 1925 noted that if the dye was injected into animals it would first appear around the cardiac and pyloric ends of the stomach. This suggested the acid secreting cells were not factors in the excretion of neutral red. However, in 1934, Davidson,

\*New England Medical Center Gastro-Intestinal Clinic of the Boston Dispensary.  
Submitted June 15, 1941.

and Henning both published papers in which the mechanism was more correctly stated.

Davidson (6), working with animals, noted that the dye appeared only on top of the rugae in the fundus region. In cases of achlorhydria in humans he failed to note the dye and therefore felt that the acid secreting cells excreted the dye.

Henning (7), however, made direct microscopic studies on living animals and obtained proof by direct visualization that the dye was excreted by the pepsin cells in its alkaline yellow color and that as it passed upward in each tubule it encountered the acid secreting cells and turned red. He further showed that the dye could be excreted in the absence of acid secreting cells.

This is consistent with the work by Faber (8), Pollard et al who showed that pepsin secreting cells may be present even with histamine achlorhydria such as is found in pernicious anemia.

Because the gastroscope offered a means of observing both the time and the site of appearance of neutral red in the gastric mucosa (10) such observations were carried out concomitant with routine gastroscopic examinations.

Thirty patients, comprising an unselected group, received injections of the dye. Forty mgms. of neutral red in one cc. of sterile water was injected either intravenously or intramuscularly into fasting patients prepared for gastroscopy.

In sixteen of the cases the dye appeared. In fourteen cases no dye was seen. This does not mean that it was not excreted. The following factors may have been responsible for the failure to visualize the dye. (1) Most of these cases had an alkaline fasting

secretion. (2) The period of observation might have been too short. (3) Some of the patients had received atropine as pre-medication.

In those cases where the dye appeared the time of appearance varied from three to forty minutes. There was no correlation between the degree of acidity (alcohol test meal) and the appearance time.

The dye usually appeared as pinpoint areas of red which diffused very slowly. The number of such points were never more than twelve and were scattered. The sites of appearance were limited to the fundus and upper body with a predilection for the anterior and posterior walls. No dye was seen at the cardia, antrum, or pylorus.

This would appear to indicate that:

(a) few of the pepsin and hydrochloric acid secreting cells were functioning during the fasting state of the stomach;

(b) the site of dye excretion in the fasting state is limited to scattered areas in the fundus.

## REFERENCES

1. Fuhl: Briefkasten. *Munchen med. Wchnschr.* 55:224, Oct. 1907.
2. Finkelstein, R.: Excretion of Dye Through the Stomach. *J. Verdauungsst.* 39:229-231, Jan. 1923.
3. Grewer, K. and Wittgenstein, H.: Chromoscopic Studies of Gastric Secretion. *Klin. Wchnschr.* 2:1650, Aug. 23, 1923.
4. Hirabayashi: Chromodiagnosis of Secretory Disturbances of Stomach. *Arch. J. Verdauungsst.* 33:71-76, April, 1924.
5. Pierol, G. M., Roelke, H. L. and Bank, J.: The Practical Value of Neutral Red as a Test for Gastric Secretory Function. *Am. J. Med. Sci.* 176:405-415, Sept., 1925.
6. Davidson, Perry B., Wilcox, E. and Haagenbach, C. D.: Gastric Excretion of Neutral Red. *J. A. M. A.* 55:794-797, Sept. 11, 1925.
7. Henning, N.: Die Entzündung Des Magens. 1922.
8. Faber, K.: Gastritis and Its Consequences. 184 pp.
9. Pollard, W. S. and Bloomfield, A. L.: Gastric Acidities in Relation to Disease. 1933.
10. Personal Observation by Dr. H. Lerner and Dr. A. Wieting. 1935.

# The Prognostic Significance of the Blood Urea Nitrogen Following Hematemesis or Melena

By

LEON SCHIFF, M.D., RICHARD J. STEVENS, M.D.\*

and

HAROLD K. MOSS, M.D.\*

with the technical assistance of

ELLEN S. GARBET, M.S.

CINCINNATI, OHIO

IN the past few years attention has been called to the frequency of azotemia following massive hemorrhage from the upper part of the digestive tract and to the prognostic value of this phenomenon, facts which we have confirmed in a recent study† (1). This azotemia unlike that associated with high intestinal obstruction may occur in the absence of any vomiting, that is, in the presence of melena only, and is accompanied by a normal or increased blood chloride

concentration and a normal carbon dioxide combining power of the blood.

Following a single non-fatal hemorrhage, the blood urea nitrogen may rise within a few hours, reach a maximum within twenty-four to forty-eight hours, and drop to normal on the third or fourth day (1). In the event of further hemorrhage not proving fatal a secondary rise may occur. In fatal cases with repeated or continued hemorrhage an increasingly or persistently high blood urea nitrogen concentration is noted.

We believe the digestion of the blood filtered in the intestinal tract and the absorption of the digestive products to be the most important factor in the production of the elevation of the blood urea nitrogen which follows hematemesis (2). The degree of azotemia depends chiefly on the amount of blood

\*From A. Hoffman Fellow in Internal Medicine, 1932-1933 and 1934-1935 respectively.

This study was aided in a grant from Parke, Davis & Company through the generosity of Dr. F. A. Kober.

From the Department of Internal Medicine, University of Cincinnati College of Medicine and the Gastro Laboratory of the Cincinnati General Hospital.

Read before the Section on Gastro-Enterology and Proctology at the annual session of the American Medical Association, New York City, June 15, 1935.

†This report constitutes a brief review of the literature. Published June 20, 1935.

# PROBABLE CAUSES OF HEMORRHAGE IN 135 PATIENTS WITH HEMATEMESIS OR MELENA

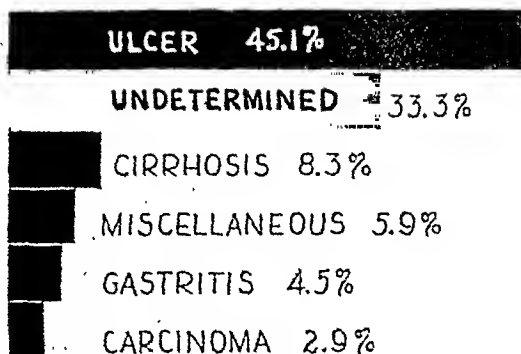


Chart I

caping from the circulation and the rate at which this blood enters the upper part of the digestive tract. The lack of a constant relationship between the rise in urea nitrogen and the fall in red cells is explained by the frequency of gradual bleeding as occurs, for example, in patients who have tarry stools for days preceding hematemesis. The factor of renal insufficiency is not essential to the increase in blood urea nitrogen, although it may play a role particularly in the presence of shock (3).

We have extended our original study of fifty-three cases to one hundred and thirty-five admissions among one hundred and nineteen patients,\* covering a period between October 1, 1937, and May 1, 1940. The cases were, with one exception, observed at the Cincinnati General Hospital and were treated with a modified Meulengracht diet (4). The determinations of the urea nitrogen were, in most instances, carried out in duplicate on oxalated whole blood by means of the aeration method of Van Slyke and Cullen (5). The first specimens were obtained immediately after admission of the patient to the hospital before the administration of any food or fluid. Later specimens were generally obtained under fasting conditions although in some instances the blood was obtained shortly after a meal, usually breakfast. Since MacKay and MacKay (6) have shown that single meals containing a usual amount of protein have only a minor effect on the concentration of urea in the blood, it was considered unnecessary to obtain all specimens under fasting conditions.

The distribution of the probable causes of hemorrhage in this series is given in Chart I. Diagnoses were based on clinical, X-ray and gastroscopic examination, and, in thirty-three patients, on operation or autopsy. The ulcers included gastric, duodenal and anastomotic lesions and were in every instance demonstrated by X-ray, gastroscopy, operation, or necropsy. Gastritis was considered to be the source of bleeding only when a definite erosion was demonstrable. The largeness of the group of cases with bleeding of undetermined origin may be explained by the frequency of negative X-ray findings and the absence of erosions on gastroscopic examination (which was usually

carried out ten days to two weeks after hemorrhage). The miscellaneous group included two cases of ruptured aortic aneurysm, one each of gastric neurinoma, duodenal carcinoma, pancreatic carcinoma, esophagitis, and thrombocytopenic purpura.

The age distribution is given in Table I. Approximately half the patients (seventy) were fifty years of age or over.

Most of the patients in this series had severe bleeding. In one hundred and twenty-one or 89.6 per cent, the minimum red cell count was under 3.5 million (Table II).

A maximum blood urea nitrogen value of 30 mg. per cent or more was obtained in seventy-eight or

TABLE I  
*Age of patients*  
(135 cases of hematemesis or melena)

| Age            | No. of Cases  |
|----------------|---------------|
| Below 30 years | 13 )          |
| 30-39          | 23 ) 65 cases |
| 40-49          | 29 )          |
| 50-59          | 44 )          |
| 60-69          | 22 ) 70 cases |
| 70-79          | 4 )           |

57.7 per cent of the one hundred and thirty-five cases. In twenty-six or 19.2 per cent of the cases an elevation of 50 mg. per cent or more was present. Fifty-five of the patients included in this study were admitted within twenty-four hours of the first observation of hemorrhage, twenty-seven on the second day, and eighteen on the third day, making a total of one hundred cases seen within the first three days of hemorrhage. Sixty-five of these one hundred cases had a blood urea nitrogen content of 30 mg. per cent or more.

There were no deaths in fifty-five cases with a maximum blood urea nitrogen of less than 30 mg. per

TABLE II  
*Minimum red cell counts in one hundred and thirty-five cases of hematemesis or melena*

| R.B.C. (millions) | No. of Cases     |
|-------------------|------------------|
| 0.5-0.9           | 4 )              |
| 1.0-1.9           | 56 ) 121 = 89.6% |
| 2.0-2.9           | 46 )             |
| 3.0-3.4           | 15 )             |
| 3.5-3.9           | 8                |
| 4.0-5.0           | 6                |

cent (Table III). The mortality was 16.9 per cent in those showing a level of 30 mg. per cent or more, 34.6 in those with a concentration of 50 mg. per cent or higher, and 63.6 per cent in those with a concentration of 70 mg. per cent or more. It should be noted that two of the cases with a urea concentration of above 100 and another with a urea concentration between 70 and 99 had renal disease which may have exaggerated the degree of azotemia. Only one of these three patients died following hemorrhage. In the absence of renal disease six of eight patients with a blood urea nitrogen concentration exceeding 70 mg. per cent died.

\*Ten of the patients were admitted twice and three of the patients were admitted three times.

When the entire series of patients is grouped according to the diseases responsible for hemorrhage as shown in Table IV, it is seen that the highest percentage of deaths occurred in those patients with hepatic cirrhosis who had an elevated blood urea nitrogen (in five out of eight). Death also occurred in seven of thirty-five patients with ulcer and elevated blood urea nitrogen content, although in one of these cases death was actually due to perforation which followed hemorrhage. Deaths in the two instances of hematemesis occurring in the absence of azotemia were due to ruptured aortic aneurysm.

In our previous study we reported that there was no direct relation between the age of the patient and the degree of maximum elevation of the blood urea nitrogen. When one includes only those patients seen within three days of the onset of bleeding and those who bled severely (that is, had a minimum red cell count of 3.5 million or less), it is seen that the mean maximum values for the blood urea nitrogen are highest in the sixth, seventh and eighth decades as shown by Chart II which is based on eighty-eight such

TABLE III

Maximum values for blood urea nitrogen and mortality from hemorrhage in cases of hematemesis or melena (132 cases\*)

| Blood Urea Nitrogen mg. 100 cc. | No. of Cases | No. of Deaths | % Mortality Cases with B.U.N. of |                |                |
|---------------------------------|--------------|---------------|----------------------------------|----------------|----------------|
|                                 |              |               | 70 mg. or over                   | 50 mg. or over | 30 mg. or over |
| 150 and above                   | 6            | 5             | 83.3                             |                |                |
| 70-150                          | 5            | 2             |                                  |                |                |
| 65-70                           | 7            | 1             |                                  | 14.3           |                |
| 50-65                           | 8            | 1             |                                  |                |                |
| 45-50                           | 25           | 2             |                                  |                | 8.0            |
| 30-45                           | 31           | 2             |                                  |                |                |
| Below 30                        | 55           | 6             |                                  |                |                |

\*Two cases of ruptured aortic aneurysm and one of peptic ulcer with perforation are excluded.

cases. This is in keeping with the generally recognized relationship between age and mortality in cases of hematemesis and melena.

Our present study confirms a previous statement (1) that shock\* is not essential to the elevation of the blood urea nitrogen content following hematemesis or melena. The mortality from hematemesis or melena was higher when both shock and an elevated blood urea nitrogen were present than when azotemia occurred in the absence of shock (Chart III). On the other hand, the presence of shock was apparently of no prognostic significance in the absence of azotemia.

Curves of the blood urea nitrogen in fourteen fatal cases in which repeated or continued hemorrhage occurred (Chart IV) are in sharp contrast to those obtained following a single, non-fatal hemorrhage (1). Instead of attaining a maximum concentration within twenty-four to forty-eight hours and then dropping sharply, the blood urea nitrogen generally remains at an abnormally high concentration with some fluctuation or continues to rise. In one instance, case 23, the curve resembles that seen in non-fatal cases. This

\*The syndrome of shock was a systemic blood pressure of 90 mm. or less, pulse rate of 120 or more, and a red cell count of 3.5 million or less.

TABLE IV

Blood urea nitrogen and mortality from hematemesis or melena (135 cases)

|               | B.U.N.<br>30 mg. or more |        | B.U.N.<br>Less than 30 mg. |        |
|---------------|--------------------------|--------|----------------------------|--------|
|               | No. Cases                | Deaths | No. Cases                  | Deaths |
| Peptic ulcer  | 35                       | 7      | 5                          | 0      |
| Undetermined  | 26                       | 1      | 18                         | 2      |
| Cirrhosis     | 4                        | 5      | 3                          | 0      |
| Gastritis     | 4                        | 0      | 2                          | 0      |
| Carcinoma     | 1                        | 0      | 4                          | 0      |
| Miscellaneous | 4                        | 1      | 7                          | 0      |

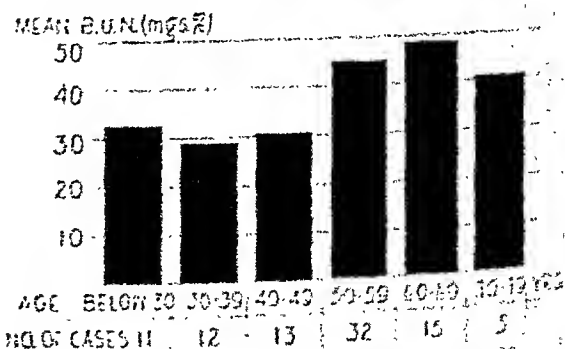
\*One patient with peptic ulcer died of perforation.  
\*Deaths due to ruptured aortic aneurysm.

patient had only one hemorrhage and died of hepatic insufficiency rather than of exsanguination. In cases 33 and 112 death was due to sudden exsanguination as a result of ruptured aortic aneurysm. The intestinal tract of case 38 contained no old blood. Permission for necropsy was not obtained in case 112.

## SUMMARY

The blood urea nitrogen was elevated to 30 mg. per cent or more in about two-thirds and to 50 mg. per cent or more in about one-fifth of one hundred and thirty-five cases of hematemesis or melena due to various causes. In no instance of hematemesis due to peptic ulcer, hepatic cirrhosis, gastritis, carcinoma, or undetermined cause, did death occur as the result of the hemorrhage in the absence of an increased blood urea nitrogen content. In the presence of azotemia five of eight patients with hepatic cirrhosis died as did seven among thirty-five patients with peptic ulcer (including one patient who died of perforation). In the presence of azotemia shock increased the mortality rate in patients with hematemesis or melena. The mean maximum blood urea nitrogen was higher in patients fifty years of age or over than in those below this age limit. In patients with repeated or continued hemorrhages which proved fatal the already elevated blood urea nitrogen generally continued to rise or

## RELATION OF MEAN MAXIMUM BLOOD UREA NITROGEN AND AGE (88 CASES)\*



\*ALL CASES SEEN WITHIN FIRST THREE DAYS OF HEMORRHAGE AND WITH 2.5 MILLION R.B.C. OR LESS

Chart II

CHART III

Prognostic significance of shock with and without elevated blood urea nitrogen\* (132 cases)†

|               | B.U.N.<br>of 30 mg. % or More        | B.U.N.<br>of Less Than 30 mg. % |
|---------------|--------------------------------------|---------------------------------|
| Shock present | Mortality = 25%<br>(8 of 32 cases)   | Mortality = 0<br>(7 cases)      |
| Shock absent  | Mortality = 11.1%<br>(5 of 45 cases) | Mortality = 0<br>(45 cases)     |

\*Value of B.U.N. represents maximum concentration.

†Two cases of ruptured aortic aneurysm and one of perforated peptic ulcer are excluded.

fluctuated above normal limits instead of reaching a maximum concentration in twenty-four to forty-eight hours and then dropping to normal on the third or fourth day as in patients with a single non-fatal hemorrhage.

### CONCLUSIONS

A blood urea nitrogen concentration of less than 30 mg. per cent in patients with hematemesis due to peptic ulcer, hepatic cirrhosis, or undetermined cause is a favorable prognostic sign.

The presence of a blood urea nitrogen content of 50 mg. per cent or more following hematemesis or melena is accompanied by a fatal outcome in one-third of cases. An elevation of 70 mg. per cent or more is accompanied by a fatal outcome in about two-thirds of cases.

Elevation of the blood urea nitrogen is particularly ominous following hematemesis in patients with hepatic cirrhosis.

The presence of shock increases the mortality rate in patients with azotemia following hematemesis or melena.

In the presence of a single hemorrhage a blood urea nitrogen curve which reaches its maximum within twenty-four to forty-eight hours and then drops to normal on the third or fourth day is almost always a favorable prognostic sign.

In the presence of repeated hemorrhage a blood urea nitrogen curve which continues to rise or remains abnormally elevated is usually associated with a fatal outcome.

### REFERENCES

1. Schiff, L. and Stevens, R. J.: Elevation of Urea Nitrogen Content of the Blood Following Hematemesis or Melena. *Arch. Int. Med.* 64:1239-1251, Dec., 1939.
2. Schiff, L., Stevens, R. J., Goodman, S., Garber, E. and Lublin, A.: Observations on the Oral Administration of Citrated Blood in Man. I. The Effects on the Blood Urea Nitrogen. *Am. J. Dig. Dis.*, 6:597-602, Nov., 1939.

## BLOOD UREA NITROGEN DETERMINATIONS IN FATAL CASES OF HEMATEMESIS AND MELENA

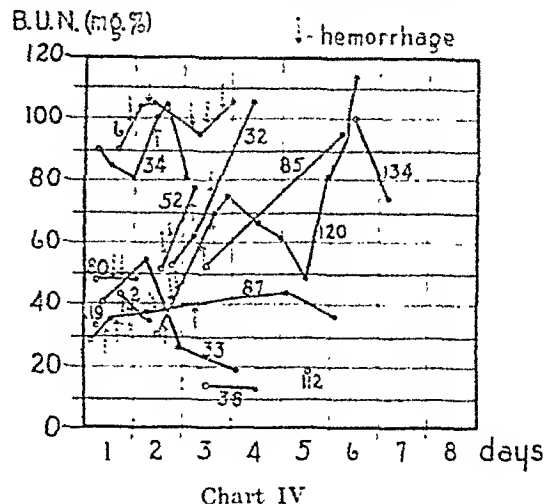


Chart IV

3. Stevens, R. J., Schiff, L., Lublin, A. and Garber, E. S.: Renal Function and the Azotemia Following Hematemesis. *J. Clin. Invest.*, 19:233-237, Jan., 1940.
4. Wits, L. J.: Haematemesis and Melena. *Brit. M. J.*, 1:547-552, 1937.
5. Van Slyke, D. D. and Cullen, G. E. in Peters, J. P. and Van Slyke, D. D.: Quantitative Clinical Chemistry. Baltimore, Williams & Wilkins Company, Vol. 2, p. 547, 1932.
6. MacKay, E. M. and MacKay, L. L.: Concentration of Urea in the Blood of Normal Individuals. *J. Clin. Invest.*, 4:295-306, 1927.

### DISCUSSION

DR. HENRY N. HARKINS (Detroit): I wish to confine my remarks to a discussion of Dr. Schiff's paper and in particular to the aspect which dealt with the causation of the azotemia.

In collaboration with Dr. Frank Chunn, I fed blood to dogs and to white rats. We obtained essentially the same results as were noted by Schiff and his associates in human beings, and by Kaump in dogs, namely that there was a marked postfeeding rise in the blood urea nitrogen. We then attempted to further isolate the factor leading to this increase, finding that the potent element in the blood in this regard is the blood cells rather than the blood plasma. In several experiments red cells given by stomach tube to dogs produced a marked rise in blood urea nitrogen while plasma produced relatively little change. Hemoglobin solutions and protein (casein) by stomach tube likewise produced a marked rise in blood urea nitrogen quite similar to that resulting from red cells.

We have concluded, therefore, that in our dogs, at least, the azotemia observed is due to absorption of blood, and in particular of the hemoglobin in the blood. We believe, therefore, that this is not only an extrarenal azotemia, but that it can be further defined. Arguing from analogy to glycosuria, we have formulated the term "alimentary azotemia" for this syndrome.

## Editorials

### CARCINOMA OF THE PANCREAS

A VALUABLE summary of present-day knowledge in regard to carcinoma of the pancreas is to be found in the September, 1941, number of the "Archives of Internal Medicine," in an article written by Dr. J. Edward Berk. Interestingly, he finds that most of the textbook writers have been wrong, and the cardinal symptom of the disease is not painless

jaundice. At the time of admission only one out of four of the patients presented this symptom. Actually, pain is so often met with that it is the commonest complaint. As the primary complaint it was found in 65 per cent of the cases. It was present at some time in 82 per cent of the cases, whereas jaundice appeared in only 71 per cent. When jaundice and pain were both present, the pain preceded the jaundice in about 85 per cent of the cases.



The pain was variable in nature. It was sometimes continuous and dull, at other times colicky and severe. It frequently radiated into the back and sometimes it was limited to the back. It was usually worse at night when the patient was lying down and was sometimes relieved if he sat up or walked about. It sometimes had an ulcer-like rhythm through the day. Interestingly, jaundice does not always occur when the head of the pancreas is involved.

Carcinoma of the pancreas is a disease that progresses fairly rapidly. On the average within six months after the appearance of the symptoms the patient is in the hospital. Loss of weight is usually rapid and severe. In Berk's series, weakness was present in three out of four cases, and nausea, vomiting and loss of appetite were noted in from 40 to 50 per cent. Interestingly, constipation was found more often than diarrhea. The gall bladder could be felt in 42 per cent of the jaundiced patients and in 24 per cent of all cases of carcinoma of the pancreas studied. Usually the liver was palpable, but a pancreatic mass could be felt in only one in eight cases. Ascites was found in only about one in nine. An impaired sugar tolerance curve was found in 78 per cent and glycosuria in 24 per cent. Anemia was usually mild. Roentgenologic signs of the disease were found in about half the cases. In about a third of the cases the titer of serum lipase was abnormally high. Occult blood was found in the stools in about 27 per cent. Fatty stools were seen in only 4 per cent. W. C. A.

#### NIGHT BLINDNESS IN SOLDIERS: A SIGN OF PSYCHONEUROSIS RATHER THAN OF AVITAMINOSIS

AS has already been pointed out in the editorial section of this Journal, although there is no question about the intimate chemical relationship between Vitamin A and visual purple, most students of the subject have been puzzled on finding that there often is but poor correlation between the degree of night blindness and the amount of Vitamin A in the diet. Evidently there are other factors that can produce this defect in vision. Because night blindness can be a serious defect in the soldier, sailor or aviator, who now has to do so much of his moving about in complete darkness, Army medical men are becoming more and more interested in the problem.

In the "British Medical Journal" for October 25 and November 1, 1941, are articles by Wittkower, Rodger, Scott and Semeonoff, who studied a group of fifty-two soldiers who were picked out for investigation when it was found that they became confused and demoralized when sent out into the dark where they couldn't see well. The instrument used for testing dark adaptation was the Nagel adaptometer.

Interestingly, the authors concluded that among normal persons, a higher level of intelligence and education and a lower age are associated with superior adaptation to the dark. In only one of the soldiers in the group studied could the investigators find an ocular cause for the night blindness. In none of them could evidence be found of Vitamin A deficiency, and the conclusion arrived at was that "most cases of night-blindness seen in this country are probably of psychologic origin. The value of dark-adaptation tests

for the discovery of night-blind patients and as an indicator of Vitamin A deficiency appears doubtful." W. C. A.

#### STUDIES ON INTESTINAL DIGESTION WITH A NEW TECHNIC

IN the December number of the "American Journal of Physiology" is an interesting article by Was-teney, Crocker and Hamilton on digestion in the small intestine of the dog. The writers have devised a technic for by-passing intestinal contents from one fistula to another a short distance caudad. Whenever desired, samples can be taken for analysis. The animals live in good health for a few months.

One of the first discoveries made with this technic was that barium, when added to a meal, goes through the gut considerably faster than food does. For instance, in one experiment, barium disappeared from the small bowel in approximately four hours, while food was still coming along five hours later.

Another interesting observation was that the extent of digestion, the volume of chyme, and the time for passage of a meal were modified by the addition of fat or meat extracts. It may be that out of further studies with this technic will come information which will help the physician in the treatment of that type of diarrhea in which material goes through the small bowel too fast. W. C. A.

#### REPORT OF THE COMMITTEE ON MILITARY PREPAREDNESS

At this time when every able-bodied physician is wondering what he can do and should do in the way of serving either his government or his community, the following report by Col. John L. Kantor is of much interest and value. It will doubtless be studied by every reader of this Journal. W. C. A.

#### COMMITTEE ON MILITARY PREPAREDNESS

January 25, 1942.

To the President and Governing Board  
American Gastro-Enterological Association  
Atlantic City, New Jersey.  
Gentlemen:

I have the honor to present the following report of the Committee on Military Preparedness, this constituting the third report made since the Committee's appointment on June 14, 1940 (previous reports January 6, 1941 and May 3, 1941).

1. *Changes in Personnel of this Committee.* The composition of this Committee remains the same as in 1940 with the following exceptions: Dr. Russell S. Boles replaces Dr. Andrew C. Ivy, ex-officio, Dr. Sara M. Jordan replaces Dr. J. Arnold Borgen as Secretary, Section on Gastro-Enterology and Proctology of the American Medical Association, but Dr. Borgen remains as regional representative. Dr. Rudolf Schindler has been added because of his experience with military medicine in Germany and his special knowledge of gastroscopy.

2. *Procedure for Recommendation of Gastro-Enterologists by the American Gastro-Enterological Association.* The procedure remains the same as previously described (American Journal of Digestive Diseases, 8:26-28, 1941). Recently a new authority has been interposed, namely the Procurement and As-

# Portal Cirrhosis With Ascites: An Analysis of 200 Cases With Special Reference to Prognosis and Treatment\*

By

RALPH G. FLEMING, M.D.†

and

ALBERT M. SNELL, M.D.‡

ROCHESTER, MINNESOTA

PREVIOUS to 1938 the general plan of treatment employed at the Mayo Clinic for patients suffering from decompensated portal cirrhosis consisted of a high carbohydrate diet, with various diuretic agents to combat ascites in selected cases. More recently, patients who have cirrhosis have received concentrates of all the vitamins together with a high carbohydrate and protein diet, while the diuretic agents have been used sparingly if at all. Many patients have shown remarkable improvement on the latter regimen. In order

portal cirrhosis with ascites is not necessarily a specific pathologic entity, but that frequently it represents the end stage of a number of diffuse hepatic lesions.

## INCIDENCE ACCORDING TO AGE AND SEX

The youngest patient was twelve years old and the oldest was seventy-eight years old. The average age of the 200 patients was 50.4 years. A study of the distribution according to age reveals that the most patients were in the fifth and sixth decades (Table I). There were 150 males and fifty females, a ratio of 3:1. Boles and Clark (1) reported 243 cases, in which 153 patients were males and ninety patients were females, and most of the patients were in the sixth and seventh decades.

TABLE I

*Distribution of portal cirrhosis according to age (200 cases)*

| Age, Years | Patients |
|------------|----------|
| 0-9        | 0        |
| 10-19      | 3        |
| 20-29      | 11       |
| 30-39      | 25       |
| 40-49      | 56       |
| 50-59      | 68       |
| 60-69      | 29       |
| 70-79      | 8        |

## CAUSATION: CONTRIBUTING FACTORS

We have no intention of entering into the much-disputed question of the causation of portal cirrhosis, but we present the following as the most likely factors in the production of the disease process in the particular group in question. In eighty-five, or 42.5 per cent, of the 200 cases the condition was considered to be alcoholic in origin (Table II). Alcohol and syphilis were combined factors in production of the disease in seventeen, or 8.5 per cent of the cases and in fifteen,

to have a basis for comparison of the results to be expected from the two methods of treatment, a study was made of 200 patients treated at the clinic from January, 1930, to December, 1939, inclusive. In addition, a special inquiry was made as to the prognosis in cirrhosis of the liver after the onset of ascites.

## MATERIAL

Two hundred cases in which we feel certain that the diagnosis of portal cirrhosis with ascites was correct were selected. In any case in which there was a possibility that the diagnosis might have been confused with a cardiac or renal lesion, chronic peritonitis and abdominal carcinomatosis, such a case was excluded. The diagnosis was confirmed by operation, necropsy or peritoneoscopy in seventy-six of the 200 cases. Included in this series are a number of cases of so-called Banti's disease and also a few in which the clinical picture of portal cirrhosis was present and in which positive results to serologic tests for syphilis were obtained. We realize that such a procedure in selection may be criticized, but it is our belief that

TABLE II

*Etiologic factors in portal cirrhosis (200 cases)*

| Factor               | Cases, Number |
|----------------------|---------------|
| Alcohol              | 85            |
| Alcohol and syphilis | 17            |
| Syphilis             | 15            |
| Banti's disease      | 6             |
| Uncertain            | 77            |
| Total                | 200           |

or 7.5 per cent, of the cases the condition was classified as "syphilitic cirrhosis." In six, or 3 per cent, of the cases the condition was associated with Banti's disease. It is seen that alcohol, a factor in eighty-five cases, or 42.5 per cent, was the most likely etiologic agent. A total of 102 patients (51 per cent) gave a history of having consumed alcoholic beverages in excessive amounts. These observations correspond somewhat to those reported by other authors. Schumacher (2) noted that in forty-five cases of diffuse hepatic

\*Read before the meeting of the Minnesota Society of Internal Medicine, Minneapolis, Minnesota, May 17, 1941.

†Fellow in Internal Medicine, Mayo Foundation.

‡Division of Medicine, Mayo Clinic.

cirrhosis diagnosed at necropsy at the New York Hospital, there was presumptive evidence of syphilis in about 28.8 per cent; approximately a third of the patients during life were known to have used alcohol to excess and in 11.1 per cent of the cases both syphilitic and alcoholic conditions had been present. Evans and Gray (3) of California reported, on the basis of study of 217 cases of cirrhosis of the liver, that forty-six (26.5 per cent) of 173 patients from whom an adequate history was obtainable had consumed alcohol to excess, and also that there had been a definite increase in Laënnec's cirrhosis in the proportion of three to one since repeal of the national prohibition law. Syphilis was an associated condition in twenty-six (12 per cent) of the total group of cases reported by the aforementioned writers. Chapman, Rowntree and one of us (Snell (4)) reported that of fifty-eight patients who had compensated cirrhosis, twenty-five had used alcohol freely or excessively, and ten (17.2 per cent) had given a history or had had some physical or serologic signs of syphilis.

In three cases of our group inorganic arsenic possibly was an etiologic agent. One patient was a heavy user of alcohol, but gave a history of having taken Fowler's solution daily for about a year before the onset of ascites. Results of analysis of the urine and nails were negative for arsenic, but 12 gm. of hair contained .06 mg. of this element. In the other two cases results of urinalysis were positive for arsenic. For one of the patients the diagnosis of chronic arsenic poisoning had been made at the Mayo Clinic in 1927, and in October, 1930, the patient had noticed the onset of ascites. Much has been written concerning the relationship between antisyphilitic treatment and portal cirrhosis, but we were unable to say definitely that treatment with arsenicals was a factor in the production of cirrhosis in any of our cases in which patients had been treated for syphilis.

In spite of the reports mentioned herein and numerous similar ones, there is no uniform agreement in the question of whether or not alcohol and syphilis have any relationship to the production of cirrhosis of the liver. Connor (5) possibly has added the connecting link to the unsolved question of the theory of the role of alcohol in the production of cirrhosis by stating that most alcoholic persons eat an abnormal diet, a circumstance which, in conjunction with the large quantities of alcohol ingested, produces a fatty condition of the liver that eventually develops into portal cirrhosis.

### SYMPTOMS AND SIGNS

The symptomatology and results of physical examination in a case of advanced portal cirrhosis constitute a very characteristic picture and need little comment. A large percentage of these patients gave a history of indigestion of several years' duration, constipation or diarrhea, vague indeterminate pain in the upper part of the abdomen and attacks of jaundice, before the onset of the symptoms and signs that were recognized as being caused by portal cirrhosis. This was not always true, since in about a fourth of the cases the first abnormal factors noticed by the patient were edema of the ankles and enlargement of the abdomen. Loss of weight and weakness were complained of frequently, and in 40 per cent of this group of patients one or more attacks of jaundice had oc-

curred, which probably represented periods of progressive hepatic damage. From 13.5 per cent of the patients a history of gastro-intestinal hemorrhage was elicited. This figure probably is lower than would be expected in such cases as were included in this study.

One hundred and ninety-four of the 200 patients presented evidence of abdominal ascites on physical examination (Table III.) The remaining six had

TABLE III  
*Symptoms and signs of portal cirrhosis (200 cases)*

| Symptoms                     | Instances | Signs                          | Instances |
|------------------------------|-----------|--------------------------------|-----------|
| Loss of weight               | 117       | Abdominal distention           | 194       |
| Asthenia                     | 104       | Edema of extremities           | 116       |
| Abdominal pain               | 92        | Enlarged liver                 | 163       |
| Edema of extremities         | 91        | Jaundice                       | 91        |
| Jaundice                     | 80        | Visible collateral circulation | 62        |
| Indigestion                  | 59        |                                |           |
| Constipation                 | 46        | Palpable spleen                | 51        |
| Diarrhea                     | 36        |                                |           |
| Gastro-intestinal hemorrhage | 27        |                                |           |

fluid which was either noted at operation or later was one of the outstanding signs of the patient's disease after the patient left the clinic. The liver was palpable in 54.5 per cent, and the spleen in 31.5 per cent of the cases. No doubt these organs more frequently would have been found to be enlarged if ascites had not been present (especially enlargement of the spleen, which is always a very significant and helpful diagnostic feature in this disease.) In 45.5 per cent of the cases clinical evidence of jaundice was present and in 31 per cent of the cases distended superficial abdominal veins were present. With a fairly typical history and the presence of the aforementioned signs, the diagnosis is relatively simple.

### PROGNOSIS IN PORTAL CIRRHOSIS AFTER THE ONSET OF ASCITES

A review of the literature immediately impresses the observer with the fact that the outlook for a patient who has portal cirrhosis after there is evidence of decompensation has always been regarded as very poor. In 1863, Flint (6) reported that in forty-six cases of hydroperitoneum in which the condition was suspected of being due to cirrhosis of the liver, twenty-four patients were known to be dead, that the duration of the disease from the onset of dropsy in these cases varied from six weeks to seventeen months, and that the average duration of the disease in sixteen of the patients was five months. In the nineteenth century the general opinion of most clinicians as to the fatality of this disease can be summed up in the words of White (7) . . . "I have not been able to find a single case among the sources from which I have drawn those collected here, in any way showing that we can look for any other end than speedy death when once ascites has developed." He reviewed twenty-four cases of alcoholic cirrhosis, in ten of which the

patients died about two months after the abdomen had first begun to swell and before paracentesis was necessary. Paracentesis was performed for the remaining fourteen, but none lived long enough to require a second abdominal tapping, and in twelve of these cases there were sufficient data to permit estimation of the time that had elapsed between the onset of abdominal distention and death: the average period was sixty-three days. Bristow (8) was one early dissenter from this generally held opinion; he was "certain that in no inconsiderable minority of such cases recovery takes place under suitable treatment." In 1931 Chapman, Rowntree and one of us (Snell) (9), reported a series of 112 cases of decompensated portal cirrhosis in which at the time of writing eighty-four patients had died and twenty-eight had lived for an average of sixteen and thirty-eight months, respectively, after the onset of ascites. These results were encouraging

to be expected during the first year after the appearance of decompensation, and once this period has passed, the patients have an excellent chance of a long survival or even of "cure." To interpret this observation, it seems that it must be assumed that if any degree of regeneration or repair of the liver is possible, it should be apparent within a year, and if regenerative processes once begin, regeneration may be sufficiently great to maintain the patient's life and health for a long period.

The immediate cause of death was obtained in fifty-four of the 158 cases in which the patients died. Twenty-three patients died of hepatic insufficiency, fifteen of gastro-intestinal hemorrhage, fourteen from some infectious process, one from a pulmonary embolus and one from apoplexy. Seven of these fifty-four patients died within a few days after operation; four died from hepatic coma, one from gastro-intestinal hemorrhage and one of generalized peritonitis.

### RESULTS OF TREATMENT

One hundred and fifty patients selected for study were treated between January, 1930, and January, 1938.\* Of this group of patients 143 received all or part of routine medical treatment that consisted of a special diet that was high in carbohydrates, low in fat, protein and certain minerals. The intake of fluids was limited to 800 to 1200 cc. in twenty-four hours. Ammonium chloride or ammonium nitrate was administered orally in doses of 5 to 12 gm. daily and one of the various mercurial diuretic agents was injected intravenously at intervals of two to four days. In addition, the majority received glucose intravenously repeatedly during their stay in the hospital. Eighty underwent paracentesis once or more at the clinic, and syphilitic patients received specific treatment, usually potassium iodide and mercury, administered by mouth. Twenty-four patients underwent omentopexy.

Among the 143 patients who we considered had adequate medical treatment, good results were obtained for forty-four (30.8 per cent), as characterized by a gain in strength, diminished ascites and prolongation of the expectancy of life. Several patients in this group seem to have obtained permanent cure at the time this report was completed. Forty patients (28 per cent) obtained fair results; these patients exhibited signs of temporary improvement and responded well to the administration of diuretic agents, but soon experienced relapse and there was no evidence that the progress of the disease had been altered, although many of these patients lived for many months. Fifty-nine (41.2 per cent) patients exhibited no favorable response, but continued to become worse and expired within a short time after treatment had begun.

By the time our study of these 150 patients had been completed, 128 were dead and only twenty-two were living. Forty per cent died within three months after coming to the clinic, 58 per cent were dead by the end of six months and 68.6 per cent did not survive for a year. It is impossible to say that any of the patients who were alive at the time this report was completed were cured, but twelve were in excellent health, requiring neither medication nor paracentesis,

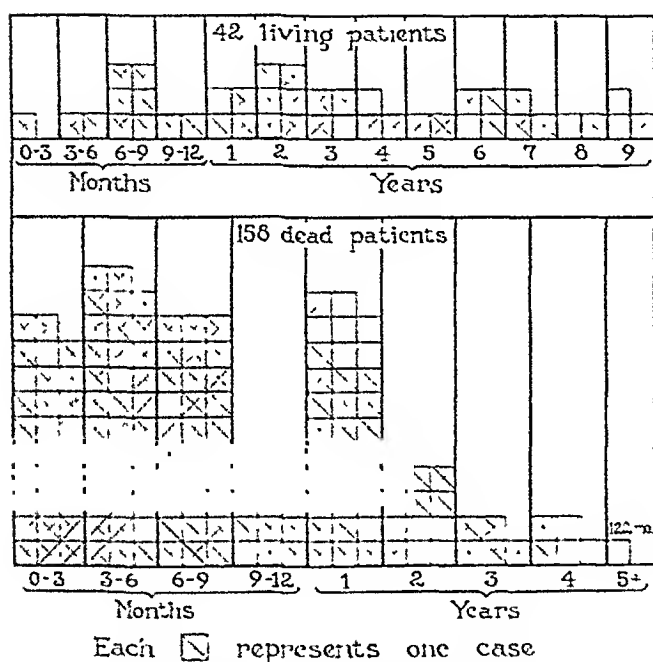


Fig. 1. Prognosis in portal cirrhosis after onset of ascites.

on a comparative basis, and made it appear that the effort expended in the treatment of such patients was not altogether hopeless.

At the time our study was completed 158 patients were dead and forty-two were living (Fig. 1.) The average duration of life of the 158 dead patients after the first appearance of abdominal distention was 12.9 months, and the forty-two living patients had survived for an average of 45.5 months at the time this report was completed. In Fig. 1 is shown the number of patients who are living and the number who have expired within certain monthly and yearly intervals after the onset of ascites. One hundred and three died during the first year, thirty-two died during the second year and twenty-three of the patients who have died lived longer than two years. Of the forty-two patients who were alive at the time this report was completed, only eleven had not survived for as long as a year after the onset of ascites, four had lived from a year to two years and twenty-seven had lived longer than two years. These results indicate clearly that the greatest mortality rate (greater than 50 per cent) is

\*As mentioned previously, the entire series comprised 200 cases and the patients were encountered between January, 1930, and January, 1940.

and were living a normal life. Two patients still required ammonium nitrate and mercurial diuretic agents, to control the ascites, and seven patients, although they were in fairly good condition, required abdominal tapping at intervals of two to four weeks. Definite information concerning one living patient could not be obtained.

Results obtained with the form of therapy thus far considered were fairly satisfactory, but it was evident that considerable care would have to be made in selection of cases in which diuretic agents were to be used. Toxic reactions, consisting of diarrhea, fever and microscopic hematuria, occur frequently, and the forced administration of such agents in cases in which no immediate increase in urinary output occurs often seems to precipitate the onset of the fatal hepatorenal syndrome. The presence of a marked degree of jaundice, gastro-intestinal bleeding and mental confusion is definitely a contraindication to the use of diuretic agents and if they are used there is always the possibility of increasing the degree of acidosis among older patients who have moderate renal insufficiency.

During the past few years many new contributions have been made concerning the physiologic aspects of the liver, and several clinical observations appeared which indicated that the therapeutics for portal cirrhosis should be changed. The data accumulated on the mechanics of transudation in the presence of hepatic disease seem to indicate that ascites and edema are dependent on a disturbance of the hydrostatic pressure of the portal venous system and the colloidal osmotic pressure of the blood serum. It has been generally assumed that portal hypertension exists, but it has never been measured directly among living patients suffering from cirrhosis of the liver. McIndoe (10) perfused cirrhotic livers removed at necropsy with a physiologic solution of sodium chloride at a pressure of 260 to 400 mm. of water, and observed that only about a third of the fluid was forced through the venous system. Thompson and his collaborators (11) measured the pressure in the splenic vein in the presence of Banti's disease and found the average pressure to be 360 mm. of water. These readings of pressure represented an enormous increase as compared with the normal pressure of 125 mm. of water. Butt, Keys and one of us (Snell (12)) found the colloidal osmotic pressure of the blood serum of patients suffering from cirrhosis of the liver to be reduced frequently to half the normal value, and there was some degree of correlation between the amount of serum albumin and the colloidal osmotic pressure. Such an imbalance between these two opposing factors is ideal for the development of ascites; thus, the problem of correction of this abnormality presents itself. The only satisfactory method for reduction of portal hypertension depends on improvement of the status of the parenchyma of the liver. Omentopexy has been accorded a thorough trial without encouraging results. Elevation of the colloidal osmotic pressure appears to be the logical approach, and since it has been shown repeatedly that the serum proteins and especially the albumin fraction are usually reduced in the presence of this condition, it is obvious that a relatively high dietary intake of protein would be advisable. This has been avoided in the past because of the observations of Bollman and Mann

(13) that pronounced ascites would develop in animals that had experimental biliary obstruction or extensive cirrhosis produced by carbon tetrachloride when the animals ingested a diet of meat or when they were fed water-soluble extracts of meat. Recently, Bollman (14) has found that the administration of milk, egg or vegetable protein has no harmful effects.

The relationship of the liver to the storage and absorption of vitamins, and the necessity for certain vitamins in maintenance of the normal histologic structure and function of hepatic cells has attracted considerable attention. Elvehjem and his co-workers (15) found that the hepatic factor that is necessary for the cure and prevention of blacktongue in dogs is the potential supply of nicotinic acid of the liver. György and Goldblatt (16) noted that the livers of rats maintained on a diet deficient in the Vitamin B complex exhibited parenchymatous and fatty degeneration, focal and massive necrosis, hyperemia and hemorrhage and in some instances peribulbar and condensation fibrosis. These changes were preventable by the addition of yeast or yeast extract to the diet and the authors referred to suggested that deficiency of a part of the Vitamin B<sub>2</sub> complex was responsible for this pathologic picture. Rhoads and Miller (17) observed that the ability of the liver to excrete intravenously injected bilirubin was reduced in dogs when the animals were fed on a diet lacking the Vitamin B complex, that this function could be restored to normal by the feeding of a normal diet, and that the function could be partly restored by the administration of liver extract. The studies of Muss, Bersey and Hastings (18) on rats provided with a diet deficient in Vitamin B<sub>6</sub> showed that the consumption of oxygen of the liver was reduced 24 per cent and that fatty infiltration of the livers could be demonstrated on microscopic examination. Halliday (19) found that the livers of rats that were maintained on a diet lacking in Vitamin B<sub>6</sub> were heavier and contained a higher percentage of total fatty acids than livers of animals that had ingested a normal diet. Sebrell and Onstott (20) were able to produce cardiac arrhythmia, bradycardia, collapse, coma and rapid death in dogs ingesting a low-riboflavin diet; and at necropsy yellow mottling of the liver and degenerative changes in the central nervous system were observed. All these changes could be prevented by the early administration of riboflavin. Also, evidence exists to suggest that the Vitamin B complex indirectly plays an important role in the mechanism by means of which glucose is transformed into glycogen, since the five respiratory enzymes of Warburg and Christian (21), which are thought to influence this reaction, each contains a molecule of riboflavin. Rich and Hamilton (22) were able to produce in rabbits cirrhosis of the liver that resembled Laënnec's cirrhosis in man, when the animals were fed a diet lacking yeast.

On the basis of these experimental observations it appears obvious that certain vitamins influence the normal function of the liver and that in the presence of severe hepatic damage improper utilization of these substances would be expected. Clinical signs of vitamin deficiency as characterized by glossitis, peripheral neuritis, night blindness, anemia and pellagra dermatitis are not infrequently encountered among patients suffering from severe hepatic damage and it



seems reasonable to expect that the administration of large doses of the vitamins might influence the symptoms, signs, course and prognosis of hepatic disease. Field (23) observed that administration of the Vitamin B complex would increase the concentration of the plasma proteins and decrease the degree of edema and ascites. Patek (24) reported encouraging results after thirteen patients suffering from alcoholic cirrhosis had been treated with vitamin concentrates; ten patients in his study improved steadily and only three died. Six patients were relieved of abdominal distention and anasarca. The serum albumin of eleven patients was increased and hepatic function as indicated by the bromsulphthalein test improved in five.

Several of these observations gradually stimulated interest in alteration of the regimen of treatment, and since early in 1938 the majority of our patients suffering from cirrhosis of the liver have been provided with a diet consisting of 350 to 500 gm. of carbohydrate, 110 gm. of protein (chiefly of vegetable origin or derived from milk and egg white) and approximately 50 gm. of fat. Vitamin supplements have been employed in large doses, such as usually, 30 minims of oleum percomorphum and 9 to 12 fluid-ounces (266 to 355 cc.) of orange juice daily (in some cases two to four vita-kaps and 100 mg. of cevitamic acid have been substituted), 2 fluid ounces (59 cc.) of a liver extract\* daily or 2 cc. of a liver extract (campolon) intramuscularly three times a week, two to four tablets of brewers' yeast with each meal and 4 to 10 mg. of thiamine chloride daily, administered parenterally or by mouth. Recently, liquid yeast concentrates have been used providing considerably larger doses of the Vitamin B complex. Some patients have received nicotinic acid. The majority received glucose intravenously while under treatment in the hospital and the syphilitic patients were treated with additional specific drugs. Abdominal paracentesis was performed when necessary and occasionally a 10 per cent solution of a mercurial diuretic agent (salyrgan) and ammonium nitrate were employed for those patients who were considered to be excellent candidates for therapy with diuretic agents.

Fifty cases in which treatment had been carried out according to this general plan were selected. One of these patients had omentopexy performed. Many of the patients were not advised to take the exact doses of vitamins mentioned previously but nevertheless received sufficient quantities, so that we felt justified in including them in this group. In addition, there were several instances in which the high protein diet was not prescribed, although there was no contraindication to its use. When this particular part of the study was completed, thirty patients were dead and twenty were living. Forty-four per cent of the fifty patients had improved remarkably, and the remaining patients exhibited no evidence that the course of the disease had been altered. The average duration of life after coming to the clinic for treatment of the thirty patients who died was 4.1 months. This figure is discouraging when it is noted that the 128 dead patients in the group the members of which received diuretic agents died on an average of 8.3 months after registration at the clinic. Of the twenty patients who survived, eleven were en-

joying very good health at the time this report was completed, ascites had disappeared and it seemed that these patients were on the road to recovery. Five patients reported that they were much better and that the degree of ascites was gradually diminishing; the remaining four patients had not improved and the frequency of the need for paracentesis and the amount of fluid present had not been altered.

In comparison of the results of treatment in the two groups of patients, it seemed evident that the use of a high protein diet, the addition of vitamin concentrates and the avoidance of diuretic agents (except for patients who reacted promptly and favorably to their use) had a favorable influence on the course of the disease. Of the fifty patients treated in this manner, 22 per cent were free of ascites or fluid was accumulating so slowly that they might be regarded as approaching the state of "compensation." This is in distinct contrast to the earlier group of 150 patients who received diuretic remedies as the principal feature of therapy; of this group only 8 per cent had recovered at the time of this report. The mortality rates for the first year of the disease are not materially different in the two groups of cases: in fact, the average duration of life of patients who died was longer in the larger group. Since the diagnostic criteria established were the same in the two groups one cannot attribute this to a difference in the stage of the disease at the time diagnosis was made. It seems more rational to assume that there was about an equal proportion of patients in both groups who had hepatic lesions so extensive that little prospect of recovery remained. It is, of course, well known that if the portal circulation is sufficiently reduced there is small likelihood of regeneration of hepatic parenchyma. This fact doubtless explains the irreversible nature of the disease in more than half of all cases studied. The "cures" probably are to be expected chiefly among patients who present various degrees of fatty metamorphosis, degeneration and necrosis without extensive periportal fibrosis and great restriction of portal blood flow. A number of the favorable results in the smaller and more recently treated group of fifty patients were obtained for patients who had large livers, with moderate degrees of retention of bromsulphthalein and a relatively short history of ascites. With early diagnosis and a consistent and vigorous program of treatment, better results seem certain to be obtained. Obviously, only the passage of time will allow for the complete evaluation of the high protein—high vitamin intake plan of therapy. The statistical data thus far obtained and the sound physiologic basis on which the therapy was established seem to justify continued use of the particular form of therapy under consideration.

#### SURGICAL TREATMENT

The surgical treatment for ascites associated with cirrhosis of the liver has in general proved to be a failure, although varying results have been reported. White (25) in 1906 reviewed a series of 227 collected cases in which omentopexy had been performed and noted that eighty-four patients had been cured, twenty-nine had improved, that the treatment had been a failure for thirty-four patients and that seventy-five patients had died soon after the operation. In 1922 Gibbon and Flick (26) reported the

\*Valentine Company, Inc.



results of operation in ten cases: four patients died within a period of about three months post-operatively, four were relieved of ascites and there was no definite change in the condition of the other two. Grinnell (27) found that in twenty-two cases in which patients had been followed after omentopexy (the complete series constituted thirty-three patients) two patients were symptom-free, seven were improved and thirteen displayed no improvement. Six of these thirteen patients died within eleven days of the operation and the deaths were classified as "operative."

Of the twenty-five patients in our study who underwent omentopexy, fifteen died on an average of 2.2 months after the operation and four of these deaths were considered to be "post-operative." Two patients died of hepatic insufficiency, one of gastro-intestinal hemorrhage and coma and one of generalized peritonitis. Of the remaining ten patients six died on an average of 24.6 months post-operatively and none of these patients had displayed any signs of definite improvement. Four patients were still living; one of them had lived eighty-four months, one of them had lived fifty-six months, one had lived sixty-eight months and one had lived seven months, post-operatively at the time this report was completed. Three of these four patients still required abdominal tapping

frequently; one had not required paracentesis either before or after operation. On the basis of these observations it would appear that omentopexy cannot be recommended.

### SUMMARY

In our study, alcohol was the most frequently encountered contributing etiologic factor. Fifty-one per cent of the patients gave a history of the consumption of alcoholic beverages in excessive amounts.

The average duration of life for the 158 patients who died after the onset of ascites was 12.9 months; the forty-two patients who were alive at the completion of this study had survived for an average of 45.5 months.

The most frequent causes of immediate death were coma, gastro-intestinal hemorrhage and infection.

Satisfactory results of treatment were obtained for 30.7 per cent of the patients who received a high carbohydrate diet and diuretic agents, as compared to excellent results for 44 per cent in the group that received a high carbohydrate, high vegetable protein diet and large doses of vitamins.

Diuretic remedies, on which so much therapeutic reliance has been placed in the past, probably do more harm than good except in selected cases.

Omentopexy for ascites proved to be a failure.

### REFERENCES

- Boles, R. S. and Clark, J. H.: The Role of Alcohol in Cirrhosis of the Liver; a Clinical and Pathologic Study Based on Four Thousand Autopsies. *J. A. M. A.*, 107:1200-1203, Oct. 10, 1936.
- Schumacher, G. A.: Causative Factor in the Production of Laennec's Cirrhosis with Special Reference to Syphilis. *Am. J. Med. Sci.*, 194:693-700, Nov., 1937.
- Evans, Newton and Gray, P. A.: Laennec's Cirrhosis: Report of 217 Cases. *J. A. M. A.*, 110:1159-1161, April 9, 1938.
- Chapman, C. H., Snell, A. M. and Rowntree, L. G.: Compensated Cirrhosis of the Liver: a Plea for More Intensive Consideration of the Earlier Stages of Disease of the Hepatic Parenchyma. *J. A. M. A.*, 109:1735-1741, June 3, 1933.
- Connor, C. L.: The Etiology and Pathogenesis of Alcoholic Cirrhosis of the Liver. *J. A. M. A.*, 112:387-390, Feb. 4, 1939.
- Flint, Austin: Clinical Report on Hydro-peritoneum, Based on an Analysis of Forty-six Cases. *Am. J. Med. Sci.*, 45:306-339, April, 1863.
- White, W. H.: The Cause and Prognosis of Ascites Due to Alcoholic Cirrhosis of the Liver, to Perihepatitis, and to Chronic Peritonitis. *Guy's Hosp. Rep.*, 49:1-42, 1892.
- Hirstow, J. S.: Observations on the Cure or Subsidence of Ascites Due to Hepatic Disease. *Brit. Med. J.*, 1:547-551, April 23, 1892.
- Chapman, C. H., Snell, A. M. and Rowntree, L. G.: Decompensated Portal Cirrhosis: Report of One Hundred and Twelve Cases. *J. A. M. A.*, 97:237-241, July 25, 1931.
- McIndoe, A. H.: Vascular Lesions of Portal Cirrhosis. *Arch. Path. and Lab. Med.*, 5:23-42, Jan., 1928.
- Thompson, W. P., Caughey, J. L., Whipple, A. O. and Rousselot, L. M.: Splenic Vein Pressure in Congestive Splenomegaly (Banti's Syndrome). *J. Clin. Invest.*, 16:571-572, July, 1937.
- Butt, H. R., Snell, A. M. and Keys, Angel: Plasma Protein in Hepatic Disease; a Study of the Colloid Osmotic Pressure of Blood Serum and of Aqueous Fluid in Various Diseases of the Liver. *Arch. Int. Med.*, 63:143-155, Jan., 1939.
- Bollman, J. L. and Mann, F. C.: Experimentally Produced Lesions of the Liver. *Ann. Int. Med.*, 5:699-712, Dec., 1931.
- Bollman, J. L.: Personal communication to the author.
- Elsehjem, C. A., Madden, R. J., Strong, F. M. and Woolley, D. W.: The Isolation and Identification of the Anti-black Toxin Factor. *J. Biol. Chem.*, 123:137-149, March, 1937.
- György, Paul and Goldblatt, Harry: Hepatic Injury on a Nutritional Basis in Rats. *J. Exper. Med.*, 70:185-192, Aug., 1937.
- Rhoads, C. P. and Miller, D. K.: Hepatic Dysfunction in Dog Fed Diets Causative of Black Tongue. *J. Exper. Med.*, 67:453-467, March, 1938.
- Muss, Jytte, Bessey, O. A. and Hastings, A. B.: Effect of Lactoflavin and Vitamin B<sub>12</sub> Deficiency on Tissue Metabolism. *J. Biol. Chem.*, 119:LXXII-LXXIII, 1937.
- Halliday, Nellie: Fatty Livers in Vitamin B<sub>12</sub> Deficient Rats. *Nutrit.*, 16:285-290, Sept., 1938.
- Sebrell, W. H. and Onstott, R. H.: Riboflavin Deficiency in Dogs. *United States Treasury Department Public Health Service*, 31: 83-91, Jan. 21, 1938.
- Warburg, Otto and Christian, Walter: Bismekunne fiber f-alk Fermente. *Biochem. Ztschr.*, 298:368-377, 1933.
- Rich, A. R. and Hamilton, J. D.: The Experimental Production of Cirrhosis of the Liver by Means of a Deficient Diet. *Johns Hopkins Hosp.*, 66:185-193, March, 1910.
- Field, Henry, Jr.: The Relation of Vitamin B to Serum Proteins and to Edema. *J. Clin. Invest.*, 16:553-564, July, 1937.
- Patek, A. J., Jr.: Treatment of Alcoholic Cirrhosis of the Liver with High Vitamin Therapy. *Proc. Soc. Exper. Biol. and Med.*, 37:329-330, Nov., 1937.
- White, Sinclair: Discussion on the Surgical Treatment of Acute Secondary to Vascular Cirrhosis of the Liver. *Brit. Med. J.*, 2:1287-1296, Nov. 10, 1906.
- Gibson, J. H. and Flick, J. B.: The Present Status of Epilepsy, with the Report of Ten Cases. *Ann. Surg.*, 75:419-424, Apr., 1922.
- Grinnell, R. S.: Omentopexy in Portal Cirrhosis of the Liver with Ascites: a Review of Twenty-three Cases. *Ann. Surg.*, 161:233-261, March, 1935.

## Two Cases of Double Gall Bladder

By

MEYER GOLOB, M.D.

and

JOHN L. KANTOR, M.D.

NEW YORK, NEW YORK

CASES of double gall bladder are extremely rare. Boyden (1) reviewed the literature from 1674 to 1926 and found only twenty instances in humans. Duplication, according to Boyden, occurred five times in 19,000 subjects, or an incidence of 0.026 per cent.

Submitted August 1, 1941.

His very extensive study of the abnormality, based on examination of 10,000 domestic mammals and upon reports covering approximately 19,000 cadavers and hospital patients, yielded 456 cases of double gall bladder, showing an incidence of 1 in 8 cats; 1 in 28 calves, 1 in 85 lambs and sheep; 1 in 198 pigs; and by

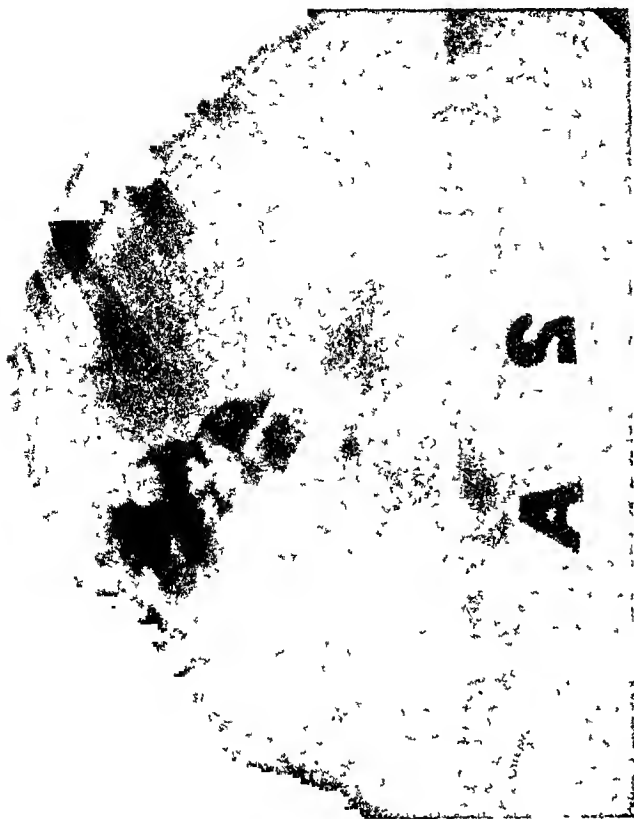


Fig. 1, Case 1. Double gall bladder filled with dye.

contrast in humans, 1 in nearly 4,000. Dr. Daniel Sasmor (21), Veterinary Inspector, U. S. Bureau of Animal Industry, states that, in ten months of cattle autopsy dealing with about 75,000 head, he encountered two cases of double gall bladder. He described one of them as follows:

"A Holstein bull, six to eight years of age, was presented. All viscera were normal with the exception of the anomaly of duplication. Each gall bladder had its own cystic duct. One was  $4\frac{1}{4}$  inches long and the other was  $2\frac{3}{4}$  inches long. Both contained normal bile."

A review of the clinical literature indicates that between 1921 and 1941, 28 articles were published on double gall bladder. Thirteen of these originated in the United States and fifteen abroad. The anomaly was apparently disclosed by operation or autopsy in 20 cases (ref. 2, 8, 9, 11, 13-20, 22-29) and by cholecystography in six cases (ref. 3-7, 12.) The cases of Holderman (14), Slaughter and Trout (22) are interesting in that the Graham test failed to visualize either of the two gall bladders, and in the case of Croudace (8), only one of the two organs appeared in the cholecystogram. The first case revealed by the Graham method was reported by Climan (6) in 1929. Our two cases, therefore, probably represent the seventh and eighth disclosed by cholecystography. In addition to those discovered by cholecystography, there is the case of Nichols referred to by Graham et al (10) in which a double gall bladder was demonstrated by finding two groups of gall stones in the radiograph. In both of our cases, roentgenologically studied, the gall bladders were pyriform and of normal size. The dye test yielded a normal sequence—the organs filled.

concentrated and emptied in response to a fat meal. The fundi of the bladders were free, as demonstrated on the films taken following a fat meal; this suggests that they were not held together by serous covering. It is conceivable from this that each gall bladder has its own cystic duct.

#### CASE REPORTS

Case 1. (M. G.) male, age 38. The symptomatology was of seven years' duration and directed attention entirely away from the diagnosis of gall bladder disease. Instead, the patient described a duodenal ulcer symptom complex with its diurnal and nocturnal pain. He was actually diagnosed as having a duodenal ulcer in Berlin, Germany, in 1934, and was discharged improved after a month's treatment on duodenal ulcer regimen. Physical examination has always been negative. After a four years' lull in symptoms, a duodenal ulcer syndrome recurred. Roentgen study by one of us (M. G.) failed to show duodenal ulcer. The gastric chemistry revealed normal acid values (free HCl 23, total acid 43), four plus mucus.

The negative duodenal X-rays and the relatively low test meal figures suggested a review of the history which disclosed jaundice at the age of ten years, and a continued history of food disagreements suggesting cholecystic disease. These findings led to study of the gall bladder (Figs. 1-2.)

Diagnostic biliary drainage obtained fragmentation of bile into A. B. C. segments, several specimens of the aspirates yielded occult blood and a duodenal tube in situ showed a distorted course.

Roentgenologically two gall bladders were demonstrated. These showed a normal sequence following ingestion of the dye and did not appear to be involved in any pathological process. There were no stone shadows. However, in view of the history and the duodenal tube findings, it is still possible that this patient is harboring a low grade cholecystitis.



Fig. 2, Case 1. Double gall bladder after fat meal.



Fig. 3, Case 2. Double gall bladder filled with dye. Note difference in dye concentration in the two gall bladders.

Case 2. (J. L. K.) woman, age 35 years. The dominant complaints were: postprandial distress with occasional gas cramps, constipation with periods of obstipation up to 12 days with accompanying generalized edema. She had no episodes of diarrhea, neither mucus nor blood was noted in the stools. There were no symptoms supporting gall bladder disease.

The essential physical findings were: an asthenic individual, 40 pounds underweight. (Actual weight 91 pounds, ideal weight 131.) Practically the entire colon was palpable and spastic, the cecocolon was tender. The right kidney was palpable, liver edge and spleen were not felt. The rectum was normal. Blood pressure readings showed hypotension (88/70.) Trousseau's sign was positive and Chvostek's sign slightly positive. The finger nails were curved. Proctoscopy showed no abnormality. Laboratory: Urine negative except for increased indican. Test meal: free HCl 30; total acidity 49, (normal figures.)

Roentgen study of the gastro-intestinal canal showed the following: The second portion of the duodenum was pulled to the right; considerable ileal stasis at 9 and 24 hours following ingestion of the barium meal; ileal emptying at 48 hours, refilling at 72 hours, and again emptying at 96 hours; unhastrated and sausage type of colon filling; appendix visualized and beaded.

Opaque enema showed a spastic distal colon but no real haustration anywhere. There was considerable reflux into the ileum, the terminal loop of which was dilated to almost the width of the cecocolon.

Cholecystography, double dose technic: One gall bladder was seen in the normal position and of normal density. Lying obliquely across it was a shadow of similar size and shape, though fainter. After the fat meal both gall bladders were shown to be emptying and appeared to be

equal in density. There were no stone shadows (Figs. 3-4.)

### DISCUSSION

Boyden classified his twenty cases of duplication of the gall bladder in humans as follows: (1) Vesica divisa, or bilateral gall bladder; (2) Vesica duplex with two cystic ducts, subdivided into a Y-shape into which the two cystic ducts unite before entering the common duct, and (3) a ductular type with two cystic ducts entering separately into the choledochus. Duplication of the viscus, with two cystic ducts is the prevailing type of anomaly as pointed out by Slaughter and Trout (22.) Seventeen of Boyden's twenty cases were of this type. It is possible that our two cases fall into this group. The case of Wischnewsky (28) was interesting in that in addition to duplication, the normal and the accessory organ were situated at a considerable distance from each other, and in that an extensive inflammation of one had not affected the other. The patient presented a clinical picture of empyema of the gall bladder. At operation the two gall bladders were discovered. The normal organ occupied the conventional site, the inflamed organ was on the left. It was the size of a large pear, filled with liquid contents, its anterior border lying at the edge of the liver.

The case of Braun (2) is strikingly similar to Wischnewsky's in that the two gall bladders were separated from each other. The gall bladder for which his patient was operated on appeared filled with calculi. Owing to the presence of adhesions, the extirpation of the viscus proved to be laborious. Suddenly bile started to flow; it came from a duct which was



Fig. 4, Case 2. Double gall bladder after fat meal.

supposed to be an accessory biliary duct. Following a cholecystectomy, further examination showed the duct to be situated, not in the region of the gall bladder, but behind some connective tissue; it was connected with a small culdesac. Microscopic examination of this organ revealed the structure of a typical gall bladder. The author remarks that, if the second gall bladder had not been discovered accidentally, a later development of calculi in the accessory gall bladder or in the biliary duct requiring a secondary operation, might have led to the conclusion that the second bladder was a neoformation. With respect to separation of the two gall bladders, Priesel (20) refers to a case seen by Kehr in 1693. This case was reported in 1693-94, in the Philosophical Transactions of London. The patient, a woman aged 31, had died of fibrous phthisis. An abnormally large liver was found, filling both hypochondria. There was a gall bladder on the right and one on the left lobe. The two organs were far apart. Pursser in 1886, saw in a girl of 11 years who died of scarlet fever, two separate gall bladders with separate cystic ducts which emptied into the common duct at some distance from each other.

The wide separations are perhaps explained by a primary double budding of the primitive gall bladder *anlage*, as the two gall bladders lay at some distance from each other. In seeking an explanation for the cases in which the two organs lie close together, Priesel refers to Schmincke, who attributes such malformations to defective formation of the lumen in the first periods of development of the organ. The lumens that develop in the solid epithelial masses do not be-

come confluent but develop independently of each other. The common, hepatic and cystic ducts early develop lumens at a time when the *Anlage* of the true gall bladder does not yet contain a lumen. This lumen probably appears in the third month of fetal life.

#### COMMENTS AND SUMMARY

When a clinical diagnosis of a diseased gall bladder has not been verified by cholecystography, the following theoretical possibilities might occur: In the first situation, operation reveals a diseased gall bladder which is removed; an anomaly is not thought of; a supernumerary viscus may still be present, and may be entirely overlooked. If the accessory organ should be diseased the results would be serious. In the second situation, a normal gall bladder is found at operation in its conventional site. Again an anomaly is not thought of. An accessory gall bladder may therefore still be the seat of trouble. The cases of Wischnewsky and Braun demonstrate some of these points; neither case was X-rayed pre-operatively, in both the bladders were separated from each other, one being normal, the other diseased. Fortunately both organs were revealed at operation.

On the other hand, if cholecystography is performed it should be borne in mind that since a diseased gall bladder may coexist with a normal accessory gall bladder, the former may not be visualized, while the latter would reveal a normal sequence.

This finding might lead to a wrong negative diagnosis, with the result that an unsuspected active lesion might be overlooked. In short, the possibility of an accessory gall bladder should always be borne in mind both pre-operatively and post-operatively.

#### REFERENCES

1. Boyden, E. A.: *Am. J. Roent.*, 33:589, 1935. *Am. J. Anat.*, 38:177, 1926.
2. Braun, A.: *Zentralbl. f. Chir.*, 53:1055, 1926.
3. Braunschweig, W.: Cholecystographic Demonstration of Double Formation in Man. *Roentgenpraxis*, 5:594-596, Aug., 1933.
4. Bryan, L.: Double Gall Bladder. Case. *Radiology*, 35:242, Aug., 1940.
5. Cave, P.: Double Gall Bladder. 2 Cases. *Lancet*, 1:751-752, April 4, 1931.
6. Cilman, M.: Duplication of Gall Bladder Demonstrated by Cholecystography. *Med. J. and Rec.*, 130:73-74, July 17, 1929.
7. Coraehan, M., Figueras, I. and Faixat, F.: Un caso de vesiga biliar doble diagnosticado radiologicamente. *Rev. de Cirugia de Barcelona*, 4:241-248, Oct., 1932.
8. Croudace, W. H. H.: Double Gall Bladder; Case. *Brit. Med. J.*, 1:707, April 25, 1931.
9. Garafalo, F.: Double Gall Bladder; Case. *Bull. d. Sc. Med.*, 5:380-385, Sept-Oct., 1927.
10. Graham, et al: Diseases of the Gall Bladder and Bile Ducts. Lea and Febiger, Philadelphia, 1928.
11. Gross, R. E.: Congenital Anomalies; Review of 118 Cases with Report of a Double Gall Bladder. *Arch. Surg.*, 32:131-162, Jan., 1936.
12. Hayes, R.: Double Gall Bladder; with Double Cystic Duct; Case. *Radiology*, 16:66-67, Jan., 1931.
13. Herrmann, S. F., Hicks, G. S. and Martin, D. L.: Double Gall Bladder; Case. *Arch. Surg.*, 27:905-909, Nov., 1933.
14. Holderman, H. H.: Double Gall Bladder. *Ann. Surg.*, 91:475-477, March, 1930.
15. Kennon, R.: Double Gall Bladder Opening by 2 Cystic Ducts Into Common Bile Duct; Case. *Brit. J. Surg.*, 20:522, Jan., 1933.
16. Meyer, A. W.: Double Gall Bladder; Case. *Deutsche Ztsch. of Chir.*, 211:404-405, 1928.
17. Millbourn, E.: Double Gall Bladder, with Report of 2 Cases. *Acta Clin. Scandinav.*, 84:97-123, 1940.
18. Minim, N. I.: Double Gall Bladder. *Vestnik Khir. (Nos. 70-71)* 24:261-265, 1931.
19. Pertinn, E.: Double Gall Bladder and Double Cystic Duct with Stone in One of Cystic Ducts; Case. *Polichinico (Sez. prat.)*, 37:1416-1417, Sept. 29, 1930.
20. Priesel, A.: Double Gall Bladder in Man; Case. *Vischow's Arch. f. path. Anat.*, 265:76-83, 1927.
21. Sasnor, D.: Personal communication.
22. Slaughter, F. G. and Trout, H. H.: Duplication of the Gall Bladder, Case Report with a Review of the Literature. *Am. J. Surg.*, 19:124, 1933.
23. Stohr, R.: Pathology of Double Gall Bladder, Case. *Zentralbl. f. Chir.*, 61:2202-2203, Sept. 22, 1934.
24. Stolkia, E.: Double Gall Bladder, Report of a Case and Review of 38. *Brit. J. Surg.*, 27:760-766, April, 1940.
25. Wakely, C. P. G.: Double Gall Bladder Removed by Operation. *Brit. J. Surg.*, 15:334-336, Oct., 1927.
26. Wilson, C. L.: Double Gall Bladder with 2 Cystic Ducts and 2 Cystic Arteries. *Ann. Surg.*, 110:60-66, July, 1939.
27. Wischnewsky, A. W.: Double Gall Bladder, Discovered During Operation, (Removal of Diseased Supernumerary Bladder). *Arch. f. Klin. Chir.*, 135:779-781, 1925.
28. Wolfson, W. L.: Supernumerary Gall Bladder. *Am. J. Surg.*, 6:88-90, Jan., 1929.

# A Self Regulatory Duodenal Mechanism for Gastric Acid Control and an Explanation for the Pathologic Gastric Physiology in Uncomplicated Duodenal Ulcer

By

HARRY SHAY, M.D., J. GERSHON-COHEN, M.D., D.Sc. (Med.)

and

SAMUEL S. FELS, LL.D.

PHILADELPHIA, PENNSYLVANIA

with the technical assistance of

HERMAN SIPLET, B.A.

THE curve of gastric acidity in the normal individual obtained by fractional gastric analysis after a standard test meal presents reasonably constant characteristics (Chart A, Curve I.) The initial drop in acidity, limited usually to the first fifteen minute extraction due to dilution by the test meal, is already well understood, as is the following rise in acidity until sixty to seventy-five minutes after administration of the test meal; but for the subsequent decrease in acidity which approaches the fasting level as the stomach empties, no completely acceptable explanation has been offered.

In the cause for this descending limb is embodied not only the mechanism for the regulation of normal gastric acidity but also an explanation for some abnormal gastric secretory pictures. While we fully realize that no abnormal gastric acid curve is diagnostic of any disease, a form of curve is sufficiently frequent in duodenal ulcer to require explanation (Chart A, Curve II.) We refer to the acidity curve rising usually to the point of complete gastric emptying, described as the extra-gastric curve.

The explanation for the control of normal gastric acid secretion has been offered through one or more of the following mechanisms.

(1) Neutralization and dilution by alkaline fluid of gastric origin. This factor has been demonstrated as of value only at the end of the secretory period when the volume of secretion is greatly diminished (1).

(2) Neutralization and dilution by fluids regurgitated from the duodenum. Although it has been clearly demonstrated in man both experimentally (2) and clinically (3) that duodenal regurgitation can be of no real significance in reducing intragastric acidity, this view persists nevertheless.

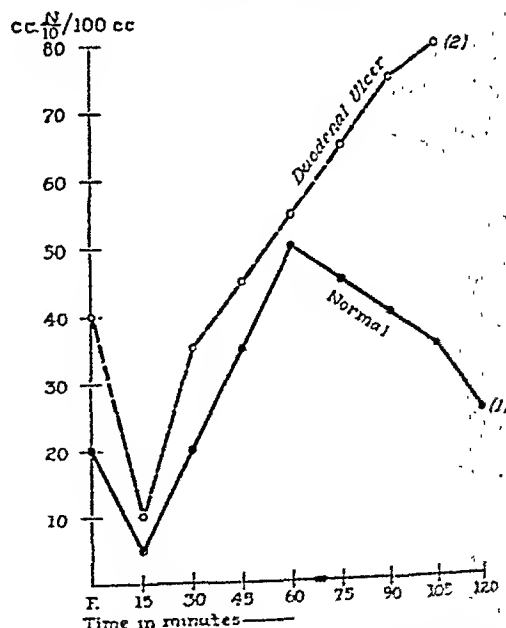
(3) An inhibition of gastric acid secretion by an intragastric mechanism.

Wilhelmj and his associates (4) from work in the dog have formulated the theory that the presence of acid in the stomach may inhibit gastric acidity. They believe that following ingestion, the partially digested food products evoke acid secretion (intragastric chemical phase) which causes an initial rapid rise in the acidity of the gastric contents. When the acidity

of the gastric contents approaches 0.06 normal (60 clinical units), inhibitory processes are set in action which operate, within the stomach, to decrease the rate of acid secretion. Between 0.06 and 0.10 normal, this inhibitory mechanism becomes increasingly active, and at 0.10 normal will inhibit completely or decrease very markedly the rate of secretion. Furthermore, since this inhibition was obtained with the whole stomach isolated from the intestine, they concluded

Chart A

Free Acid Curves.



that it was dependent upon an intragastric mechanism independent of reflex or hormone influences from the duodenum, although they did not deny that under certain conditions inhibitory effects could have their origin in the intestine. That Wilhelmj and his associates have shown such an acid inhibitory intragastric mechanism to exist for the dog is quite clear, but that a similar mechanism operates in man is not justified by human experimental data or evidence from clinical

From the Medical Research Laboratory, Samuel S. Fels Fund and the Gastro-Intestinal Division, Medical Service 1, Mt. Sinai Hospital, Philadelphia, Pa.

Submitted June 29, 1942.

pathologic-physiologic studies. Although MacLean and Griffiths (5) in 1928, propounded a theory (from their studies in man) essentially similar to that of Wilhelmj, et al, Griffiths (6) later states that the inhibition might in some way be connected with the entry of the acid gastric contents into the duodenum.

In studying the absorption of hydrochloric acid by the human stomach (7), we isolated the stomach from the duodenum for the period of experiment by maintaining pyloric closure through duodenal stimulation. We introduced into the stomach hydrochloric acid in concentrations of 0.5% and 1%. Only with the 1% acid solution was gastric secretion suppressed. With the 0.5% solution retained in the stomach, active secretion was not stopped—this when the acid concentration in the stomach was considerably higher than that reached in a normal stomach after a test meal.

Wilhelmj, O'Brien and Hill (4) consider it significant to recall that clinical observers have long maintained that 0.06 normal or 60 clinical units is approxi-

From studies (8) of the influence of fats and fatty acids instilled into the duodenum upon gastric secretion, we are convinced that there is a duodenal mechanism in man which plays an important role in the control of gastric acidity. Among many other substances besides the fatty ones studied was the duodenal instillation of hydrochloric acid in concentrations around 0.5%. With these concentrations we obtained marked depression of gastric secretion when administered simultaneously with the test meal. This suggested that the gastric acid reaching the duodenum in certain concentrations might normally be self-regulatory upon further gastric secretion; a mechanism suspected from the results of Crider and Thomas (9) and demonstrated in dogs for the psychic and intestinal phases by Day and Webster (10), and Wilhelmj, McCarthy and Hill (11). Griffiths (6) using the alcohol test meal in man also concluded that such a duodenal function exists.

We believe our data support the presence of a self-regulatory duodenal mechanism in man and furthermore in its disturbance there is an adequate explanation for the abnormal gastric secretory curve usually seen in duodenal ulcer.

# EXPERIMENTAL METHOD

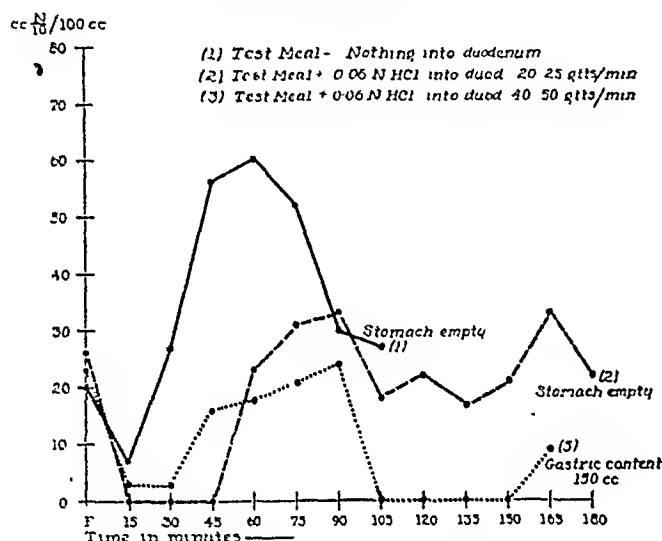
We selected patients with normal gastro-intestinal tracts showing the usual normal type of acid curve and those with proven duodenal ulcer and an extra-gastric secretory curve. Properly to test the effectiveness of the mechanism we believed to be present, we felt it should be brought into operation in a normal individual by the duodenal instillation of very small quantities of hydrochloric acid not greater in concentration than that represented by the peak of free acid following the particular gastric test meal employed. Accordingly, the patient, after an overnight fast, was intubated with two Rehfuess tubes. The tip of one was allowed to pass into the duodenum by the usual technique while the other remained in the stomach. The fasting gastric contents were removed and the test meal administered. In this study the meal consisted of 30 gms. of zweiback and 300 cc. of distilled water. Extractions were made in 10 cc. quantities at 15 minute intervals from the time the meal was started until the stomach was empty. Free hydrochloric acid, total acid, and total chlorides were determined by the usual method in each sample. This standardization procedure was repeated twice again at weekly intervals to see if our test subjects gave reasonably constant responses. If the secretory curves were within close limits of each other, the subject was selected for the test.

Curve I, Chart I is the free hydrochloric acid curve obtained in M. L., illustrative of the response obtained in the individual with a normal gastro-duodenal segment. Nothing was instilled through the duodenal tube during any standardization meal.

On another day, when a similar test meal was administered, hydrochloric acid 0.06 N was instilled through the duodenal tube at a rate of 20-25 drops per minute simultaneously with the ingestion of the test meal. Specimens were removed through the gastric tube at 15 minute intervals until the stomach was empty. Curve II, Chart I was the result obtained.

On a third day under similar conditions of experi-

Chart I  
Free Hydrochloric Acid Curves  
— Normal —

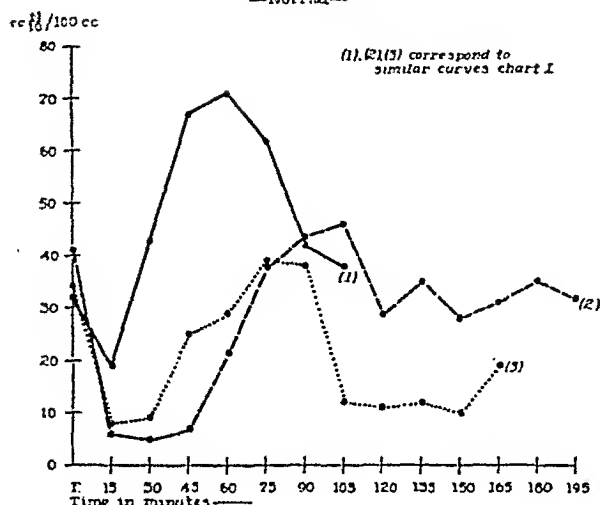


mately the normal, maximal value for the total acidity of the gastric contents during a test meal: the concentration at which inhibitory processes for acid secretion in the stomachs of their dogs were set in action. They thus imply that a similar mechanism is operative in man.

Any theory based upon animal experimentation to be applicable to human physiology must adequately explain the abnormal as well as the normal human mechanism. This the Wilhelmj theory fails to do. It may be held that the data here presented to prove that both usual and unusual ranges of gastric acidity fail to depress secretion markedly in man by their intragastric action are inconclusive. Our premise is further supported by the findings in duodenal ulcer. In this disease, though the intragastric acidity rises to much higher levels than that seen normally, no intragastric mechanism appears to inhibit secretion. If there were such an intragastric mechanism normally in man one would then have to assume a failure or marked depression of it in duodenal ulcer. There are certainly neither gross nor microscopic changes in the stomach of duodenal ulcer patients to justify this assumption.



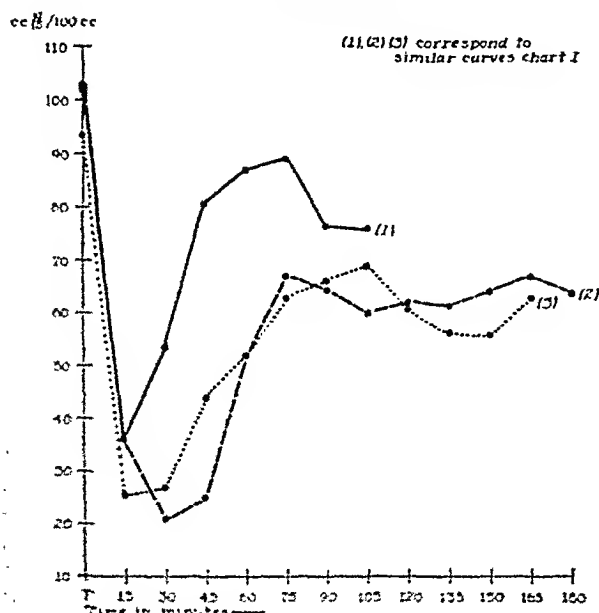
Chart II  
Total Acid Curves.  
—Normal—



mentation the hydrochloric acid 0.06 N was instilled through the duodenal tube at a rate of 40-50 drops per minute. Similar fractions of the gastric contents were removed at 15 minute intervals until 165 minutes after the test meal was started, when all of the remaining gastric contents—150 cc.—were removed (Curve III, Chart I.) Chart II represents the results during these same tests for the total acid titrated and Chart III for the total chlorides.

We did not see the dissociation of acid and total chloride curves reported by Griffiths (6). In spite of the acid depression obtained by him, Griffiths reported a continually rising concentration of total chloride which he attributed to the secretion of neutral chloride. Our chloride curves in all instances paralleled the acid curves, suggesting that the whole secretory mechanism

Chart III  
Total Chloride Curves  
—Normal—

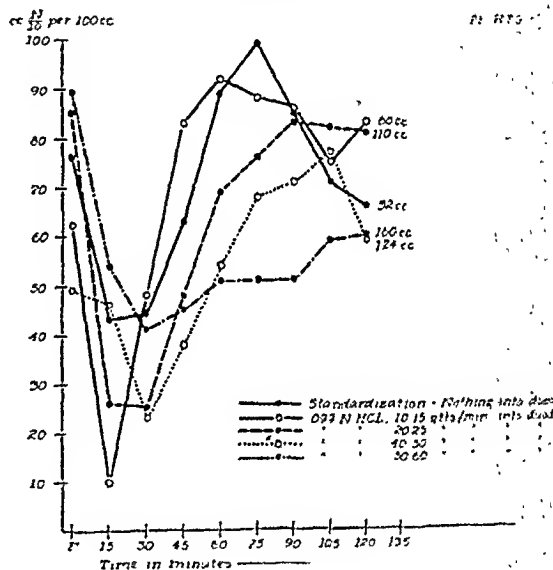


ism was affected rather than a suppression of acid and a continued secretion of chloride.

We selected 0.06 N hydrochloric acid for instillation because the peak of this patient's free acid response to the test meal alone was 60 clinical units.

The results illustrated in Charts I, II and III indicate clearly that the entrance into the duodenum of a hydrochloric acid solution similar in concentration to the peak acid response of the stomach to the particular test meal can cause a marked depression of secretory response to that test meal. In some normal individuals the duodenal instillation of their peak gastric acid concentration at 20 to 25 drops a minute appeared inadequate to demonstrate clearly the duodenal mechanism. In some cases as much as 50 to 60 drops per minute had to be instilled before the mechanism was maximally stimulated. This was particularly true in persons with normal gastro-duodenal segments with

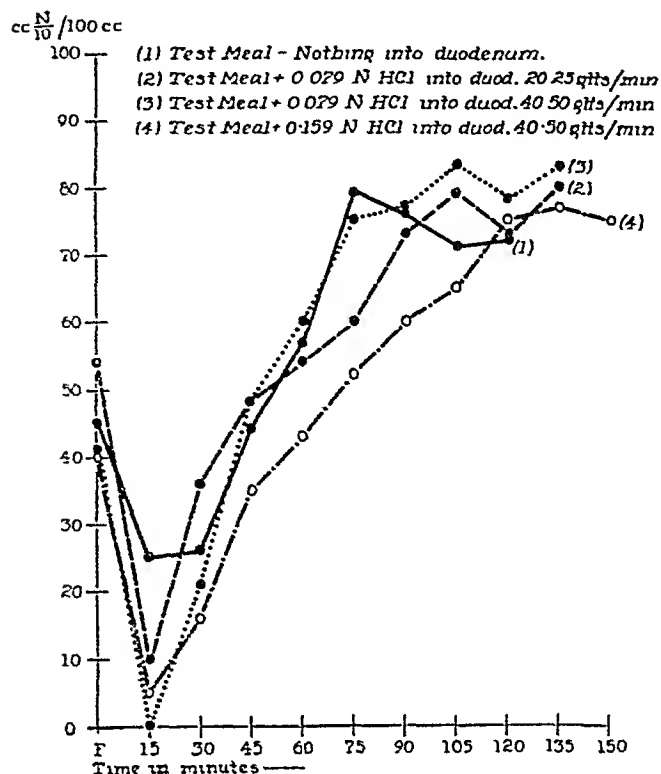
Chart B  
Free Acid Curves



a high gastric acid response. Patient W. T. G., Chart B, is a case in point. Here the duodenal instillation of his peak acidity (0.099N) at 20 to 25 drops per minute produced only a questionable depression of gastric secretion while 50-60 drops per minute produced a very striking result. We believe that this mechanism may explain the cases of low and high gastric acid response in normal individuals. If the threshold of response of the duodenal mechanism is lower than the average normal, such an individual will have a low gastric secretory response. If, on the other hand, the threshold is heightened, then a higher gastric secretory response will result.

We reported (8) previously that our data indicate the duodenal mechanism concerned with the depression of gastric secretion as especially influencing the psychic secretion in man and much less effective in depressing the chemical phase. Chart I lends further support to such a view. In the bread-and-water meal, the water may have some ability, usually slight, to

Chart IV  
Free Hydrochloric Acid Curves.  
—Duodenal Ulcer—



act as a gastric chemical stimulant (Khigine (12), Ivy (13)), while the bread has no such chemical action until it has undergone some digestion by the gastric juice (Lobassoff) (14.) Curves II and III illustrate these points. In Curve II, at 45 minutes, digestion of the bread has reached a point where it can act as a chemical stimulant for secretion. This secretion obviously is not as completely suppressed by the continued duodenal instillation of the acid, as the psychic phase has been. We get then some secretion after 45 minutes but at a much lower level than when the psychic phase operated as illustrated in Curve I. When the duodenal stimulant is increased in quantity per unit time, a relatively stronger stimulus, a somewhat more marked influence on secretion is obtained, but there is no great difference in the peaks of the chemical phases of the secretion.

Chart I, II and III also illustrate the marked effect upon gastric motor function resulting from the entrance of the hydrochloric acid solution into the duodenum, an influence which we have already fully discussed (15) elsewhere. In a previous publication we (8) have also shown that while there exists a duodenal mechanism in man which when stimulated produces both motor and secretory depression in the stomach, we showed that the threshold of response is doubtlessly different for the two effects—gastric motor function being depressed by a lesser stimulus than is necessary to cause a depression in gastric secretion. That such a difference in response should exist is quite logical. It is desirable that gastric emptying be inhibited more readily early after a meal so as to permit adequate time for gastric digestion, while gastric secretory depression should not be

brought about until enough secretion in the stomach has been assured. Thus, the normal self-regulatory gastric motor mechanism inherent in the proximal duodenum which we have previously postulated (15) operates at the lower concentrations of acid brought to it shortly after a meal is ingested while the self-regulatory duodenal mechanism for the depression of gastric secretion is activated only when the peak of acidity has been reached. In each case the intrinsic agent activating the duodenal mechanism is the gastric hydrochloric acid, but in different concentrations.

Would such a mechanism, if disturbed, adequately explain the pathologic gastric physiology in duodenal ulcer? To test this, we selected proven cases of duodenal ulcer. A solution of hydrochloric acid was prepared corresponding in concentration to the peak of their free acid response, following our test meal. At various times this solution was dripped into the duodenum under experimental conditions identical with those described above for the normal individuals. Charts IV, V and VI are illustrative of the typical results obtained.

In these cases, in addition to employing the peak concentrations of free acid for the duodenal instillate, we doubled the concentration to see if we could elicit a response. We found that in duodenal-ulcer patients duodenal instillation of a hydrochloric acid solution, even of higher concentration than that which produces a marked depression of secretion in the normal individual, produces no appreciable effect upon the gastric secretory response. Our data, we believe, show that in the duodenal ulcer patient the ulcerating process plus the associated surrounding duodenitis obtund the duo-

Chart V  
Total Acid Curves  
—Duodenal Ulcer—

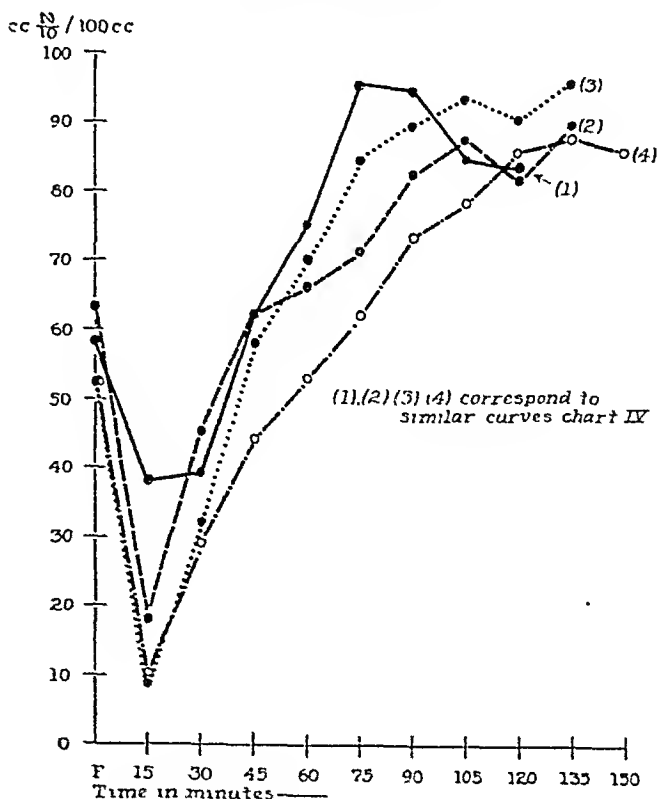
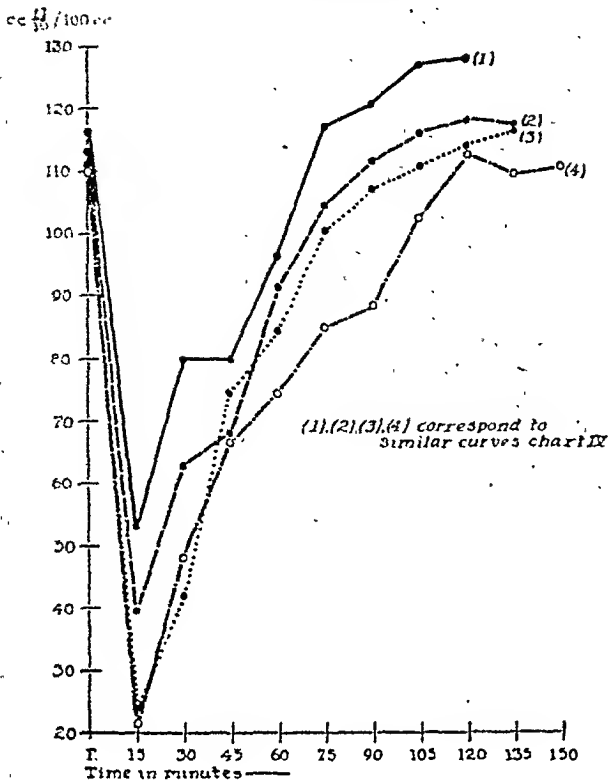


Chart VI  
Total Chloride Curves.  
—Duodenal Ulcer—



denal mechanism that normally is brought into play to reduce gastric acidity, thus allowing for the abnormally high gastric acid responses obtained after test meals in this disease.

Charts IV, V and VI also illustrate the failure in response of the duodenal mechanism as it related to gastric motor control, since no appreciable delay in gastric emptying resulted from the duodenal instillation of the acid. In the failure of this mechanism we have an explanation for another very common clinical finding in uncomplicated duodenal ulcer; namely, the rapid gastric motility. That this mechanism is dulled

only and not destroyed is shown by data previously reported, (16) since fat in the form of cream instilled into the duodenum has been shown qualitatively to influence gastric emptying in the duodenal patient as in the normal.

We have previously reported (15) that duodenal stimulation causes a depression of gastric peristalsis and tone. We thus have in the duodenal mechanism which we describe, an explanation for the normal gastric motor and secretory behavior as well as, for the first time, an adequate explanation—in this mechanism disturbed—for the characteristic clinical signs in uncomplicated duodenal ulcer; namely, hyperperistalsis, hypertonicity, hypermotility, and hypersecretion. We do not mean to ignore other mechanisms which have been shown to influence gastric motor and secretory function but we do want to stress the fact that the disturbance of this one mechanism can explain the whole clinical picture.

### SUMMARY

By a direct approach in the human subject we have demonstrated the presence in the normal duodenum of a mechanism which is brought into play by a concentration of acid peculiar to the individual. This concentration for any meal, is represented by the peak of free acidity reached after the particular meal. When this concentration of acid reaches the duodenum a mechanism is activated that depresses gastric secretion and is responsible for the descending limb of the normal gastric curve.

In the failure of the normal response of such a mechanism, obtunded by the ulceration and inflammation produced by duodenal ulcer, we believe lies the explanation for the high acid extra-gastric curve seen in this disease. That such a failure of response does occur, we have demonstrated in duodenal ulcer patients. If we combine our present findings regarding gastric secretion with the influence of the duodenum upon gastric motor function which we have previously described, we have for the first time, in the disturbance of one mechanism an explanation for the characteristic clinical gastric findings in uncomplicated duodenal ulcer—hyperperistalsis, hypertonicity, hypermotility and hypersecretion.

### REFERENCES

1. Webster, D. E.: Variations in Acidity of Gastric Juice During Secretory Period. *Am. P. Physiol.*, 90:716, 1929.
2. Shay, H., Katz, A. B. and Schloss, E. M.: Experimental Studies in Gastric Physiology I. Evaluation of the Role of Duodenal Regurgitation in the Control of Gastric Acidity in Man. *Arch. Int. Med.*, 58:705, 1932.
3. MacLagan, N. F.: Statistical Analysis of 380 Fractional Test Meals, with Special Reference to Duodenal Regurgitation. *Quart. J. Med.*, 3:321, 1934.
4. Wilhelm, C. M., O'Brien, F. T. and Hill, F. C.: The Inhibitory Influence of the Acidity of the Gastric Contents on the Secretion of Acid by the Stomach. *Am. J. Physiol.*, 115:429, 1935.
5. MacLean, H. and Griffiths, W. J.: The Automatic Regulation of Gastric Acidity. *J. Physiol.*, 66:255, 1928.
6. Griffiths, W. J.: The Duodenum and the Automatic Control of Gastric Acidity. *J. Physiol.*, 57:34, 1936.
7. Shay, H., Gershon-Cohen, J. and Fels, Samuel S.: The Absorption of Hydrochloric Acid by the Human Stomach. *Am. J. Dig. Dis.*, 1:351, 1929.
8. Shay, H., Gershon-Cohen, J. and Fels, Samuel S.: The Role of the Upper Small Intestine in the Control of Gastric Secretion: The Effect of Neutral Fat, Fatty Acid, and Soap; The Phase of Gastric Secretion Influenced and Relative Importance of the Psychic and Chemical Phases. *Ann. Int. Med.*, 13:254, 1925.
9. Crider, J. O. and Thomas, J. Earl: The Influence of Certain Conditions in the Duodenum on the Rate of Secretion and Acidity of the Gastric Juice. *Am. J. Physiol.*, 161:25, 1932.
10. Day, J. J. and Webster, D. R.: The Autoregulation of the Gastric Secretion. *Am. J. Dig. Dis. and Nutrit.*, 2:525, 1934.
11. Wilhelm, C. M., McCarthy, H. H. and Hill, F. C.: Acid Inhibition of the Intestinal and Intragastric Chemical Phases of Gastric Secretion. *Am. J. Physiol.*, 115:756, 1937.
12. Khikine, P.: Activité Secrétory de l'estomac du Chien. *Archives des Sciences Biolog.*, 3:461, 1924-25.
13. Ivy, A. C.: Contributions to the Physiology of the Stomach: Studies in Water Drinking. *Am. J. Physiol.*, 45:429, 1918.
14. Lobasoff, J. O.: Secretion Gastric Chez le Chien. *Arch. d. Sci. Biol.*, 5:125, 1896.
15. Shay, H. and Gershon-Cohen, J.: Experimental Studies in Gastric Physiology in Man. II. A Study of Pyloric Control. The Phase of Acid and Alkali. *S. G. O.*, 5:454, 1934.
16. Gershon-Cohen, J. and Shay, H.: Experimental Studies on Gastric Physiology in Man. III. A Study of Pyloric Control. The Role of Milk and Cream in the Normal and in Subjects with Quiescent Duodenal Ulcer. *Am. J. Roent. and Rad. Therapy*, 25:427, 1935.

# The Serum Coagulation Reaction: Its Clinical Significance<sup>†</sup>

By

MANFRED KRAEMER, M.D.<sup>‡</sup>  
NEWARK, NEW JERSEY

IN 1935 I (1) studied Weltmann's (2, 3) Serum Coagulation Reaction in 25 cases of liver disease and concluded that the test might be of value in differentiating between obstructive and parenchymatous jaundice. The results reported by me at that time were inaccurate in that the proper technique of reading the test was not employed. The cases used in that first study were all of advanced disease and when the test was applied in early jaundice, no differentiating values were found.

Disappointed, I ceased work with the test. No further American articles appeared until those of Levinson in 1937 (4) and 1939 (5.) After reading Levinson's first paper I was encouraged to restudy Weltmann's phenomenon. In 1940 Susan Dees (6, 7) presented her extensive studies. Her last paper should be read by all those interested in the theory and chemistry of the serum coagulation reaction. The two papers by Dr. Dees brought the literature on the test up to date.

## DESCRIPTION OF THE TEST

If blood serum is diluted in distilled water 1:50 and boiled, coagulation of the blood serum protein fails to occur. However, if a small amount of electrolyte (sodium chloride, calcium chloride, or barium chloride) is added to the diluted serum, coagulation of the serum protein takes place.

Weltmann determined that, in a boiling 1:50 dilution of normal blood serum, the lowest concentration of calcium chloride solution in which coagulation of the serum protein takes place is from .03 to .04 per cent. If 0.1 cc. of normal blood serum is added to 5 cc. of .04% calcium chloride solution and boiled, the serum protein coagulates. However if added to .02% solution of calcium chloride it fails to coagulate.

Inflammatory and exudative processes like pneumonia changed the blood serum so that the protein was coagulated in only the more highly concentrated (.08%) solutions of boiled calcium chloride. On the other hand, disease of the parenchyma of the liver, cardiac decompensation with stasis and fibrous forms of tuberculosis so changed the blood serum that the protein was coagulated in much lower dilutions of boiled calcium chloride, e.g. .02%.

## TECHNIQUE EMPLOYED

In stock is kept 500 cc. of .1% solution of calcium chloride  $\text{CaCl}_2 \cdot 6\text{H}_2\text{O}$ . Ten test tubes are placed in a row on a rack. The tubes are numbered 1 to 10 from left to right. 5 cc. of the .1% solution are added to tube one, 4.5 cc. to tube two and so on in diminishing quantity so that .5 cc. are added to tube ten. Sufficient distilled water is then added so that each tube will

contain a total of 5 cc. of solution. Thus 4.5 cc. of water are added to tube ten, 4.0 cc. to tube nine and so on in diminishing amounts to .5 cc. for tube two. Finally tube one will contain .1% solution of anhydrous calcium chloride, tube two .09% and so on down to tube ten which contains .01% solution. (I have discontinued using a tube containing .045% solution which Weltmann suggested placing between 6 and 7.)

To each test tube 0.1 cc. of the blood serum to be tested is added, this serum having been collected as for a Wassermann test. The tubes are then shaken and placed in a boiling water bath for exactly fifteen minutes. After removal from the bath, the number of tubes in which coagulation or flocculation of the serum has taken place is recorded. Coagulation is always noted in the tubes of higher concentration (tubes 1-6) and tends not to occur in tubes of lower concentration (7-10.) If there is coagulation in any tube there will be coagulation in all of the tubes of greater concentration. Thus if there is coagulation in tube 6 there must also be coagulation in tubes 1 to 5. The number of the tube containing the weakest solution in which coagulation occurs gives the reading for the test. For instance, if coagulation occurs in the first five tubes, the reading for the test is five (C.B. 5 or Weltmann 5.) This reading is called the coagulation band (C.B.) and we would report the test as C.B. 5. Care must be taken to read only the tubes in which coagulation occurs, and to disregard those with only clouding or turbidity. Clouding usually occurs in 2 or 3 tubes more dilute than the last in which true coagulation is noted. In normal serum, coagulation usually occurs in the first six tubes (C.B. 6.) If the C.B. is less than six, the C.B. is said to shift to the left, or to be shortened: if more than six, it is said to have shifted to the right or to be lengthened (Fig. 1.) Weltmann showed that in inflammatory or exudative processes, there was a shift to the left or shortening of the band and in fibrous processes and parenchymatous diseases of the liver the band was lengthened (shift to right.)

## CLINICAL MATERIAL

The test was executed over a period of two years on every private patient examined. To date 1200 tests have been performed on about 1100 patients. The test was repeated on several of the patients. In addition, 75 supposedly healthy factory executives were tested at the time of their periodic health examinations.

In addition to the Weltmann test, most of the patients had diagnostic X-ray and laboratory studies, including at least a urinalysis, Wassermann test, complete blood count and sedimentation rate (Cutler.) All but a few of the patients were ambulant. The normal range of the coagulation band is 5 to 7. This paper will concern itself only with those cases of the

<sup>†</sup>From the Presbyterian Hospital, Department of Gastro-Enterology.  
<sup>‡</sup>Miss Jacqueline Shepherd, B.S., M.T., assisted with the technical procedures.  
Submitted June 30, 1941.

TABLE 1

87 Patients in Whom the C.B. was 4 or less and Corresponding Sedimentation Rate (S.S.) (Continued)

| Number | C.B. | S.S. | Sex | Age | Diagnosis  |
|--------|------|------|-----|-----|--|
| 3241   | 4    | 27   | F.  | 36  | Ulcerative colitis   |
| 3242   | 4    | 21   | M.  | 16  | Ulcerative colitis   |
| 3243   | 4    | 22   | M.  | 40  | Active   |
| 3244   | 4    | 5    | M.  | 33  | Diabetes, duodenal ulcer   |
| 3245   | 2    | 25   | M.  | 45  | Penetrating gastric ulcer (ruptured with anastomosis operation)            |
| 3246   | 4    | 25   | F.  | 33  | Hypertensive cardiac, sinusitis  |
| 3247   | 4    | 15   | F.  | 22  | Gastric diverticulum, acute enterocolitis (upper)                          |
| 3248   | 5    | 18   | F.  | 35  | Syndrome free  |
| 3249   | 4    | 15   | F.  | 50  | Hypertensive cardiac, no complete study permitted                          |
| 3250   | 4    | 17   | M.  | 26  | Intercurrent intestinal hernia with peritoneal irritation (upper)          |
| 3251   | 4    | 19   | F.  | 21  | Acute appendicitis, chronic suppurative cholecystitis, cholangitis (upper) |
| 3252   | 4    | 26   | M.  | 47  | Focal abscess (S.S.)   |
| 3253   | 4    | 12   | F.  | 37  | Chronic suppurative cholecystitis and cholangitis (upper)                  |
| 3254   | 4    | 25   | F.  | 62  | Colonial ulcer, hypertensive cardiac (sustained cast)                      |
| 3255   | 4    | 25   | F.  | 53  | Diabetes, breast abscess   |
| 3256   | 5    | 20   | F.  | 35  | Syndrome free  |
| 3257   | 4    | 5    | F.  | 65  | Hypertensive cardiac, hypertensive cardiac (upper)                         |
| 3258   | 4    | 20   | F.  | 23  | Hypertensive cardiac, incompletely studied, chronic? food & S.S.           |
| 3259   | 4    | 15   | F.  | 57  | Colonial cholecystitis   |
| 3260   | 4    | 25   | F.  | 51  | Cholecystitis and cholangitis (upper)                                      |
| 3261   | 4    | 21   | M.  | 34  | Gastric syphilis, Escherichia & plate, neither with arsenic-saline         |
| 3262   | 4    | 10   | F.  | 37  | Acute allergic enterocolitis (proctocolitis)                               |
| 3263   | 4    | 12   | F.  | 25  | Syndrome free  |
| 3264   | 6    | 8    | F.  | 35  | Syndrome free  |
| 3265   | 5    | 15   | F.  | 57  | Penetrating gastric ulcer  |
| 3266   | 5    | 9    | F.  | 40  | Improvement (S-ray)  |
| 3267   | 4    | 27   | M.  | 25  | Lymphosarcoma of esophagus (ileostomy)                                     |
| 3268   | 5    | 25   | M.  | 42  | Appendicitis abscess (upper)   |
| 3269   | 4    | 6    | M.  | 49  | Incompletely studied, no diagnosis made                                    |
| 3270   | 4    | 12   | M.  | 23  | Pyloric ulcer (S-ray)  |
| 3271   | 4    | 6    | M.  | 24  | Colonial ulcer (S-ray)   |
| 3272   | 4    | 5    | M.  | 32  | Pyelitis   |
| 3273   | 4    | 11   | F.  | 5   | Not completely studied   |
| 3274   | 4    | 10   | F.  | 23  | Endometritis (hysterectomy)  |
| 3275   | 5    | 15   | F.  | 24  | Acute pleurisy with effusion   |
| 3276   | 6    | 15   | F.  | 27  | 12/25/40 Esophagus   |
| 3277   | 4    | 6    | F.  | 27  | Gastric cancer, central structure (proctostomy—pelvic exam.)               |
| 3278   | 4    | 15   | F.  | 25  | Colonial diverticulum (S-ray)  |
| 3279   | 4    | 27   | F.  | 25  | Cholecystitis (S-ray, biliary calculus)                                    |
| 3280   | 4    | 21   | F.  | 25  | Incompletely studied, no diagnosis   |
| 3281   | 5    | 15   | M.  | 24  | Pyelitis   |
| 3282   | 4    | 12   | M.  | 25  | Penetrating duodenal ulcer, Acute gastritis (upper)                        |
| 3283   | 5    | 26   | M.  | 40  | Incompletely studied   |
| 3284   | 5    | 25   | F.  | 57  | Cholecystitis coli, cholecystitis  |
| 3285   | 4    | 6    | M.  | 42  | Incompletely studied, possible diabetes                                    |
| 3286   | 5    | 21   | F.  | 57  | Not completely studied, history of peptic ulcer                            |
| 3287   | 2    | 25   | M.  | 44  | Cholecystitis (non-visualized gall bladder, no S-ray)                      |
| 3288   | 4    | 15   | M.  | 40  | 12/25/40 Gastric ulcer (upper)   |
| 3289   | 6    | 19   | F.  | 40  | After resection  |
| 3290   | 4    | 24   | M.  | 21  | 27/40 Vaginal cystocele with leukitis and ileitis (S-ray)                  |
| 3291   | 2    | 25   | F.  | 25  | 2/25/40 Improvement in symptoms  |
| 3292   | 4    | 21   | M.  | 52  | Penetrating duodenal ulcer (upper)   |
| 3293   | 4    | 24   | M.  | 57  | Suppurative abscess, carcinoma of liver (ileostomy)                        |
| 3294   | 4    | 20   | F.  | 44  | 12/40 Acute infectious arthritis   |
| 3295   | 6    | 7    | F.  | 40  | All symptoms gone  |
| 3296   | 2    | 21   | M.  | 42  | Ulcerating polypoid wall carcinoma of stomach (upper)                      |
| 3297   | 4    | 25   | F.  | 51  | Refractory adenocarcinoma of stomach (upper)                               |
| 3298   | 4    | 21   | M.  | 57  | Cholecystitis coli (S-ray)   |
| 3299   | 4    | 24   | M.  | 57  | Cholecystitis coli (S-ray)   |
| 3300   | 6    | 4    | F.  | 22  | 4/5/40 Ulcerative colitis  |
| 3301   | 5    | 21   | F.  | 25  | 12/25/40 Syndrome free   |
| 3302   | 4    | 27   | F.  | 42  | 12/40 Gastric cancer, carcinoma of rectum (ileostomy)                      |
| 3303   | 7    | 5    | F.  | 42  | 10/25/40 Acute resection and anastomosis                                   |
| 3304   | 4    | 25   | M.  | 35  | Hypertensive cardiac, diabetes   |
| 3305   | 4    | 27   | M.  | 27  | Cholecystitis (S-ray, visualized gall bladder)                             |
| 3306   | 0    | 25   | M.  | 15  | Local thrombosis (S-ray)   |
| 3307   | 4    | 17   | F.  | 25  | Cholecystitis and cholangitis (upper)                                      |
| 3308   | 2    | 25   | M.  | 42  | Varicella of sigmoid (upper)   |
| 3309   | 4    | 6    | F.  | 42  | Ulcerative cardiac, hypertensive cardiac                                   |
| 3310   | 4    | 15   | M.  | 57  | Cholecystitis (S-ray and biliary calculus)                                 |
| 3311   | 4    | 16   | M.  | 57  | Ulcerative colitis   |
| 3312   | 7    | 25   | F.  | 25  | 6/7/40 Ulcerative colitis  |
| 3313   | 7    | 5    | F.  | 25  | 12/41 Arrested proctologically   |
| 3314   | 4    | 25   | F.  | 57  | Cholecystitis coli   |
| 3315   | 4    | 17   | M.  | 25  | 12/41 Cholecystitis, Acute gastritis                                       |
| 3316   | 6    | 6    | F.  | 42  | 12/25/40 Improvement in symptoms   |
| 3317   | 4    | 25   | M.  | 68  | Carcinoma of colon with multiple metastases (upper)                        |
| 3318   | 4    | 15   | M.  | 64  | Carcinoma of colon (S-ray)   |
| 3319   | 5    | 14   | F.  | 21  | 12/25/40 Irritable colon, possible acute colitis                           |
| 3320   | 5    | 14   | F.  | 21  | 10/24/40   |
| 3321   | 4    | 16   | F.  | 25  | Cholecystitis and cholangitis  |
| 3322   | 4    | 15   | M.  | 25  | Cholecystitis, gastritis, Escherichia & food                               |
| 3323   | 4    | 15   | F.  | 25  | Carcinoma of stomach, gastric wall (S-ray)                                 |
| 3324   | 5    | 15   | F.  | 25  | Cholecystitis, cholecystitis, cholangitis (upper)                          |
| 3325   | 4    | 15   | F.  | 25  | Adenocarcinoma of rectum (S-ray)   |
| 3326   | 4    | 15   | F.  | 25  | Carcinoma of sigmoid   |
| 3327   | 4    | 15   | F.  | 25  | Cholecystitis (S-ray)  |
| 3328   | 4    | 15   | F.  | 25  | Refractory ulcerative colitis  |
| 3329   | 4    | 15   | F.  | 25  | Refractory ulcerative colitis  |
| 3330   | 4    | 15   | F.  | 25  | Refractory ulcerative colitis  |
| 3331   | 4    | 15   | F.  | 25  | Refractory ulcerative colitis  |
| 3332   | 4    | 15   | F.  | 25  | Refractory ulcerative colitis  |
| 3333   | 4    | 15   | F.  | 25  | Refractory ulcerative colitis  |
| 3334   | 4    | 15   | F.  | 25  | Refractory ulcerative colitis  |
| 3335   | 4    | 15   | F.  | 25  | Refractory ulcerative colitis  |
| 3336   | 4    | 15   | F.  | 25  | Refractory ulcerative colitis  |
| 3337   | 4    | 15   | F.  | 25  | Refractory ulcerative colitis  |
| 3338   | 4    | 15   | F.  | 25  | Refractory ulcerative colitis  |
| 3339   | 4    | 15   | F.  | 25  | Refractory ulcerative colitis  |
| 3340   | 4    | 15   | F.  | 25  | Refractory ulcerative colitis  |
| 3341   | 4    | 15   | F.  | 25  | Refractory ulcerative colitis  |
| 3342   | 4    | 15   | F.  | 25  | Refractory ulcerative colitis  |
| 3343   | 4    | 15   | F.  | 25  | Refractory ulcerative colitis  |
| 3344   | 4    | 15   | F.  | 25  | Refractory ulcerative colitis  |
| 3345   | 4    | 15   | F.  | 25  | Refractory ulcerative colitis  |
| 3346   | 4    | 15   | F.  | 25  | Refractory ulcerative colitis  |
| 3347   | 4    | 15   | F.  | 25  | Refractory ulcerative colitis  |
| 3348   | 4    | 15   | F.  | 25  | Refractory ulcerative colitis  |
| 3349   | 4    | 15   | F.  | 25  | Refractory ulcerative colitis  |
| 3350   | 4    | 15   | F.  | 25  | Refractory ulcerative colitis  |
| 3351   | 4    | 15   | F.  | 25  | Refractory ulcerative colitis  |
| 3352   | 4    | 15   | F.  | 25  | Refractory ulcerative colitis  |
| 3353   | 4    | 15   | F.  | 25  | Refractory ulcerative colitis  |
| 3354   | 4    | 15   | F.  | 25  | Refractory ulcerative colitis  |
| 3355   | 4    | 15   | F.  | 25  | Refractory ulcerative colitis  |
| 3356   | 4    | 15   | F.  | 25  | Refractory ulcerative colitis  |
| 3357   | 4    | 15   | F.  | 25  | Refractory ulcerative colitis  |
| 3358   | 4    | 15   | F.  | 25  | Refractory ulcerative colitis  |
| 3359   | 4    | 15   | F.  | 25  | Refractory ulcerative colitis  |
| 3360   | 4    | 15   | F.  | 25  | Refractory ulcerative colitis  |

4. Supposedly normal in Whom the C.B. was 4 or less and Corresponding Sedimentation Rate.

|      |   |    |    |    |                                  |
|------|---|----|----|----|----------------------------------|
| 3361 | 0 | 16 | M. | 47 | 5/25/40 Diabetes, Cholecystitis  |
| 3362 | 0 | 14 | M. | 47 | 12/25/40 Diabetes, Cholecystitis |
| 3363 | 0 | 14 | M. | 47 | 12/25/40 Diabetes, Cholecystitis |
| 3364 | 0 | 14 | M. | 47 | 12/25/40 Diabetes, Cholecystitis |
| 3365 | 0 | 14 | M. | 47 | 12/25/40 Diabetes, Cholecystitis |
| 3366 | 0 | 14 | M. | 47 | 12/25/40 Diabetes, Cholecystitis |
| 3367 | 0 | 14 | M. | 47 | 12/25/40 Diabetes, Cholecystitis |
| 3368 | 0 | 14 | M. | 47 | 12/25/40 Diabetes, Cholecystitis |
| 3369 | 0 | 14 | M. | 47 | 12/25/40 Diabetes, Cholecystitis |
| 3370 | 0 | 14 | M. | 47 | 12/25/40 Diabetes, Cholecystitis |
| 3371 | 0 | 14 | M. | 47 | 12/25/40 Diabetes, Cholecystitis |
| 3372 | 0 | 14 | M. | 47 | 12/25/40 Diabetes, Cholecystitis |
| 3373 | 0 | 14 | M. | 47 | 12/25/40 Diabetes, Cholecystitis |
| 3374 | 0 | 14 | M. | 47 | 12/25/40 Diabetes, Cholecystitis |
| 3375 | 0 | 14 | M. | 47 | 12/25/40 Diabetes, Cholecystitis |
| 3376 | 0 | 14 | M. | 47 | 12/25/40 Diabetes, Cholecystitis |
| 3377 | 0 | 14 | M. | 47 | 12/25/40 Diabetes, Cholecystitis |
| 3378 | 0 | 14 | M. | 47 | 12/25/40 Diabetes, Cholecystitis |
| 3379 | 0 | 14 | M. | 47 | 12/25/40 Diabetes, Cholecystitis |
| 3380 | 0 | 14 | M. | 47 | 12/25/40 Diabetes, Cholecystitis |
| 3381 | 0 | 14 | M. | 47 | 12/25/40 Diabetes, Cholecystitis |
| 3382 | 0 | 14 | M. | 47 | 12/25/40 Diabetes, Cholecystitis |
| 3383 | 0 | 14 | M. | 47 | 12/25/40 Diabetes, Cholecystitis |
| 3384 | 0 | 14 | M. | 47 | 12/25/40 Diabetes, Cholecystitis |
| 3385 | 0 | 14 | M. | 47 | 12/25/40 Diabetes, Cholecystitis |
| 3386 | 0 | 14 | M. | 47 | 12/25/40 Diabetes, Cholecystitis |
| 3387 | 0 | 14 | M. | 47 | 12/25/40 Diabetes, Cholecystitis |
| 3388 | 0 | 14 | M. | 47 | 12/25/40 Diabetes, Cholecystitis |
| 3389 | 0 | 14 | M. | 47 | 12/25/40 Diabetes, Cholecystitis |
| 3390 | 0 | 14 | M. | 47 | 12/25/40 Diabetes, Cholecystitis |
| 3391 | 0 | 14 | M. | 47 | 12/25/40 Diabetes, Cholecystitis |
| 3392 | 0 | 14 | M. | 47 | 12/25/40 Diabetes, Cholecystitis |
| 3393 | 0 | 14 | M. | 47 | 12/25/40 Diabetes, Cholecystitis |
| 3394 | 0 | 14 | M. | 47 | 12/25/40 Diabetes, Cholecystitis |
| 3395 | 0 | 14 | M. | 47 | 12/25/40 Diabetes, Cholecystitis |
| 3396 | 0 | 14 | M. | 47 | 12/25/40 Diabetes, Cholecystitis |
| 3397 | 0 | 14 | M. | 47 | 12/25/40 Diabetes, Cholecystitis |
| 3398 | 0 | 14 | M. | 47 | 12/25/40 Diabetes, Cholecystitis |
| 3399 | 0 | 14 | M. | 47 | 12/25/40 Diabetes, Cholecystitis |
| 3400 | 0 | 14 | M. | 47 | 12/25/40 Diabetes, Cholecystitis |

C.B. magnifying glass

1100 studied which had a C.B. of four or less. A more extensive analysis of the 1100 cases will appear in a subsequent article. There were 87 patients with a C.B. of four or less. Of the 75, supposedly healthy factory executives, four had a C.B. of four or less. After comparing the C.B. with the sedimentation rate, I conclude that the former has fewer variables and fewer false positive reactions. I considered a sedimentation rate of less than 12 in one hour as normal. In seemingly healthy people a C.B. of less than four will be definite evidence of the presence of an inflammatory process of the exudative type even in the absence of any symptoms or physical signs of disease. Such evidence may not be found by any other laboratory procedures now at our disposal.

By reference to the accompanying table it will be noted that diseases reducing the C.B. usually cause an increase in the sedimentation rate. However, in many instances, there is a reduction in the C.B. before the sedimentation rate is altered. In many cases when healing sets in or cure is accomplished, the C.B. returns to normal while the increase in sedimentation rate still falsely shows evidence of active inflammation.

Examination of the table reveals few and possibly no false positives. In every case sufficiently studied in which the Weltmann was four or less evidence of an exudative or malignant process could be found. While the test is not always positive for malignancy those tumors of the stomach or colon which are ulcerated will always show a reduction in the C.B. In cases 3311, 4371, 4357, 4371, 4411, 4451, 4478, 4492, 4504, 4734, 4937, and R 19, no definite diagnosis of an inflammatory process could be made. However, of these cases, numbers 3311, 4371, 4411, 4451, 4478, 4492, 4504 and 4937 were seen in the office but once.

The urine in case 4492 reduced Benedict's solution. Further study may have proven the presence of diabetes with an inflammatory complication.

Cases 4504 and 4937 gave typical histories of active peptic ulcer.

Case R 19 was not completely studied but on May 11, 1940, when the C.B. was four, he was complaining of some abdominal cramps. On November 12, 1940, when the Weltmann was five, the cramps had ceased. He

may have suffered some mild enteritis at the time of the first examination.

Case 4317 had probably had a recent coronary occlusion without symptoms.

In case 4357 a diagnosis of migraine was made when seen 7/27 39 with a Weltmann of four. On 9 13, 39 when the Weltmann was six, her headache had ceased. This was possibly a case of sinusitis which improved. That an undisclosed inflammatory process was improving is also evidenced in the decline of the sedimentation rate.

No inflammatory process was discovered in case 4734, although extensive diagnostic procedures were employed.

As has been frequently described in the literature and as we found in this study the sedimentation rate gives numerous false positives. The many variables of the sedimentation rate are not inherent to the Weltmann test.

A C.B. of four or less cannot be disregarded. A case to point is R 32. This young man was in apparent good health and had no previous history of disease. His Weltmann was three. An E.C.G. (Fig. 2) taken on 6 28 40 showed evidence of delayed conduction through the ventricles. He continued at work without symptoms. On reexamination 11/22 40 the Weltmann was six and the E.C.G. normal. This man most likely suffered an asymptomatic acute myocarditis.

The most significant finding in this report is the constancy with which the test was positive in ulcerative and inflammatory processes of the digestive tract. This fact is self evident if the table is analyzed. While there were numerous cases of duodenal ulcer with a normal Weltmann every active gastric ulcer had a C.B. of four or less. I interpret a C.B. of four or less with duodenal ulcer as evidence of penetration. Every case of ulcerative colitis with symptoms and every case of regional ileitis had a Weltmann of four or less. The constancy of a reduced C.B. in carcinoma of the stomach and colon and in posterior wall gastric ulcer has stimulated me to reinvestigation of all suspicious cases with negative roentgenologic findings. Cholecystitis almost always gave a reduction in the C.B. Diverticulitis of the colon and duodenum caused a reduction in the C.B. Asymptomatic diverticulosis caused no reduction.

#### PROGNOSTIC VALUE OF THE C.B.

As healing of an ulcerative process proceeds there is a prompt return of the C.B. to normal. The C.B. therefore becomes a valuable prognostic aid. Fig. 3

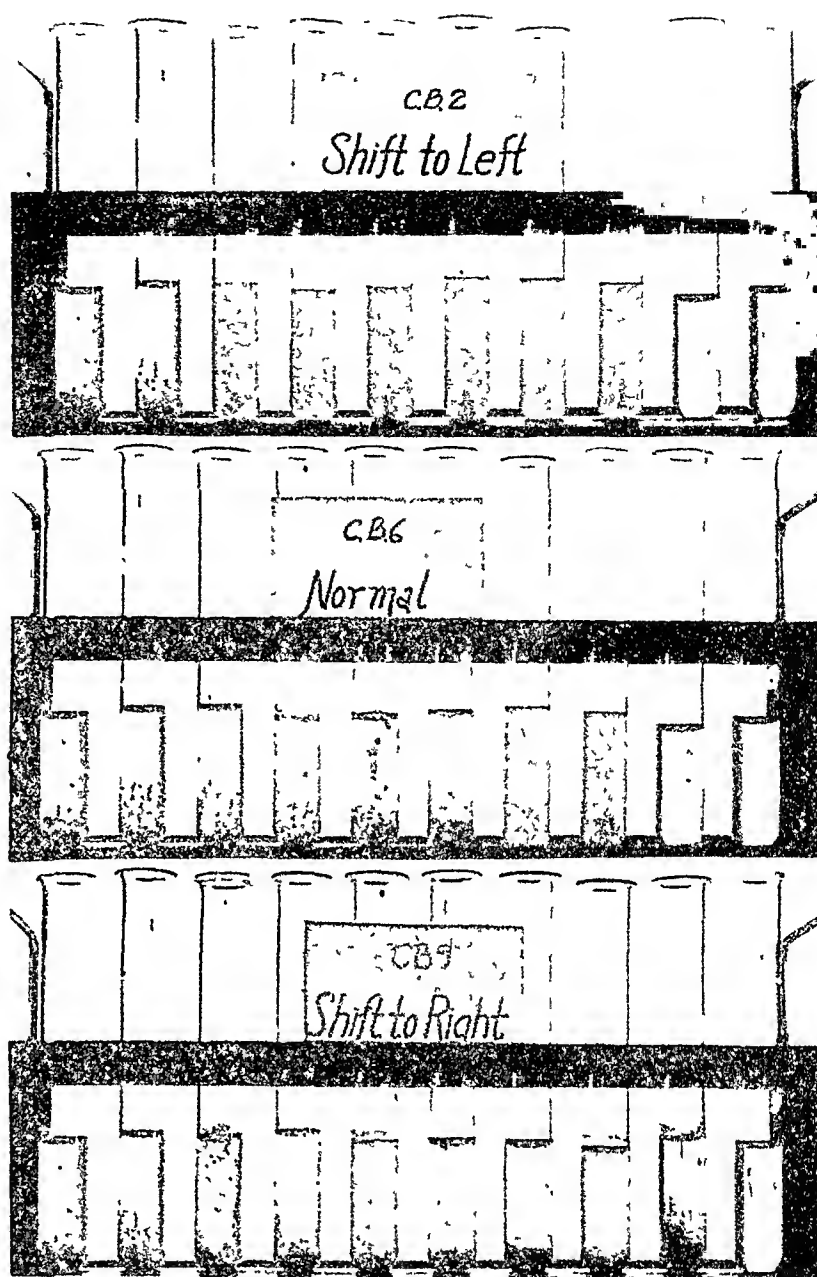


Fig. 1

(case 5005) shows the change in the C.B. accompanied the healing of a lesser curvature ulcer.

In case 4824 there was a history of an attack of acute cholecystitis. The C.B. on September 10, 1940, was four. After a series of biliary drainages, the patient became almost symptom free and pus cells disappeared from the bile. The C.B. on December 30, 1940, was normal (6.)

Case 4577 shows the improvement of the C.B. from 0 to 3 in the course of treatment of a case of Giardial dysentery. Cases 3207, 4421, 4650, 4733, 4863, 4978, and R 32 all demonstrate how the sedimentation rate returns to normal as symptoms improve.

#### COMPARISON WITH SEDIMENTATION RATE

Cases 3795, 4128, 4358, 4408, 4424, 4477, 4779, 4824, 4920, 5005, and R32 had extensive inflammatory or malignant diseases. In all of these cases the sedimen-



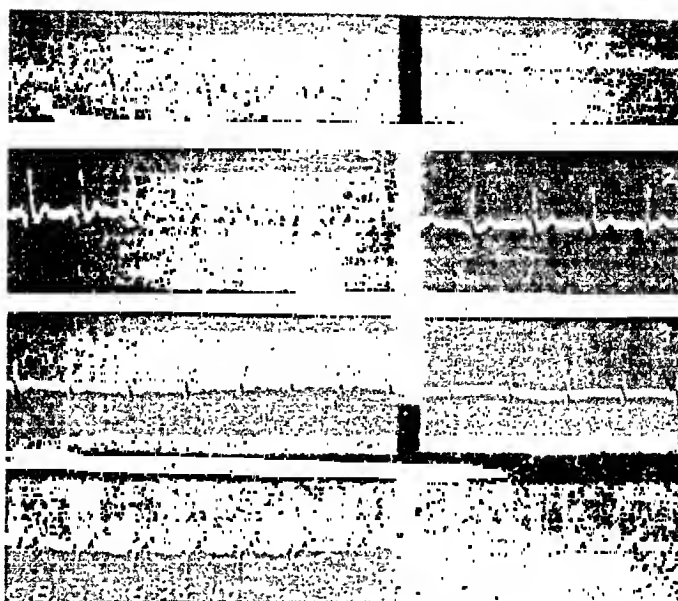


Fig. 2

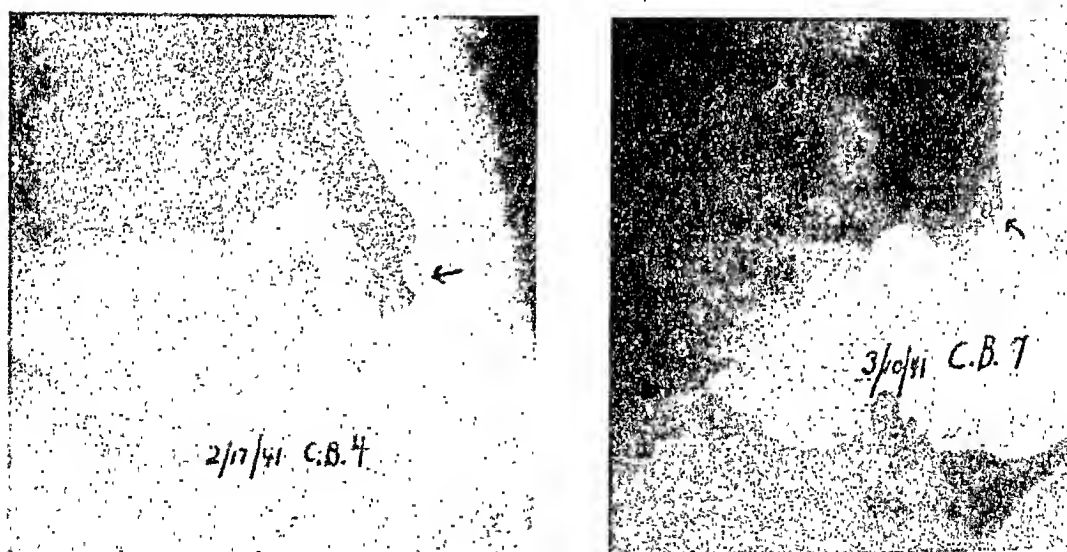


Fig. 3

tation rate was normal while the C.B. had shifted to the left.

Cases 4650 and 4944 show that the sedimentation rate may not become increased until healing sets in; when the C.B. has already returned to normal.

#### SUMMARY AND CONCLUSIONS

1. The Weltmann test is a valuable office procedure.
2. A reduction of the C.B. to four is almost certain evidence of the presence of an exudative or malignant process.
3. The Weltmann test has prognostic significance in that a return toward normal indicates healing.
4. For general use the determination of the coagulation band is of greater value than the sedimentation

rate of the red blood cells. The Weltmann reaction occurs earlier in the course of the disease. It does not have as many variables as the sedimentation rate.

#### REFERENCES

1. Kramer, M.: Weltmann Test in Diseases of the Liver. *Am. J. Dig. Dis. and Nutrit.*, 2:14, 1935.
2. Weltmann, O.: Über die Spierelung, exfoliations- und fibroser Vorrang in Blutserum. *Med. Klin.*, 2:246, 1926.
3. Weltmann, O. and Medel, C. V.: The Coagulation Band and Its Place in the Clinic. *Wien. Klin. Wochenschr.*, 12:1916, 1920.
4. Levinson, S. A., Klein, R. J. and Rosenblum, P.: The Weltmann Serum Coagulation Reaction. *Jr. Lab. and Clin. Med.*, 1937, 1937.
5. Levinson, S. A. and Klein, R. J.: The Value of the Weltmann Serum Coagulation Reaction as a Laboratory Diagnostic Test. Comparison with the Sedimentation Rate. *Ann. Int. Med.*, 12:1918, 1920.
6. Dees, S. C.: A Clinical Study of the Weltmann Serum Coagulation Reaction. *J. Ped.*, 17:11, July, 1919.
7. Ibid.: An Experimental Study of the Weltmann Serum Coagulation Reaction. *Ibid.* p. 52.

# The Use of Concentrated and Purified Antitoxic B. Coli Serum in the Treatment of Indeterminate Ulcerative Colitis<sup>\*</sup>

By

ASHER WINKELSTEIN, M.D.

and

GREGORY SHWARTZMAN, M.D.

NEW YORK, NEW YORK

## INTRODUCTION

ULCERATIVE colitis is seemingly of frequent occurrence. New studies concerning its etiology and therapy are therefore of considerable interest.

As a result of observations over a period of many years we have learned to differentiate groups among cases presenting the clinical syndrome of ulcerative colitis: (1) a small percentage is due to amoebic infection; (2) a larger number may be due to chronic bacillary dysentery in which chronic manifestations of the disease are maintained by the original *B. dysenteriae* alone or in association with some secondary bacterial invaders; (3) the remaining major number of cases belongs to an indeterminate group of unknown etiology. This communication deals with the serum therapy of the latter group designated as the "indeterminate ulcerative colitis."

The working hypothesis for the investigations about to be described was based on that part of studies on the phenomenon of local skin reactivity to bacterial filtrates which clearly demonstrated the synergistic effect of microorganisms (Shwartzman (1.)) It was shown experimentally that tissues made vulnerable through contact with the toxic filtrate of one microorganism become receptive to the severe injurious effect of toxins of a large group of apparently biologically unrelated microorganisms (among these *B. coli*, *B. influenzae*, certain strains of streptococcus, and others may be included (1.)) These observations, therefore, have brought into prominence the possible role of toxins of secondary invaders or normal bacterial inhabitants upon the evolution of diseases resulting from specific infections.

In the example of the disease under consideration, the contact of some specific microorganism, i.e., the unknown primary etiologic agent present in the bowel at the onset, may elicit a state of enhanced vulnerability to the effect of other microorganisms or their toxic products, normally present in the bowel or found elsewhere in the body. Thus, disregarding the primary etiology of the disease, the possibility has been admitted that serious damage of the disease may be superimposed and continued in the vulnerable bowel, by a secondary invader. Since *B. coli*, being one of the most common inhabitants of the bowel, was shown to elaborate potent toxins, attempts were made to determine the effect of an antitoxic *B. coli* immune serum upon severe cases of indeterminate ulcerative colitis.

The phenomenon of local skin reactivity to *B. coli*

was taken as a guide in the preparation of a good neutralizing serum, inasmuch as it enabled one to make quantitative determinations both of potent exotoxic, antigenic substances of *B. coli* culture filtrates, and the specific neutralizing values of immune sera (1.) Horses were immunized by subcutaneous injections of pooled toxins and intravenous injections of vaccines of various strains of *B. coli*. After a period of several months, sera were produced which were capable of neutralizing *B. coli* toxin in multiple proportions. The exact methods for determining the titers of these sera were previously described (1.)

In 1934, a short preliminary report on the use of unconcentrated antitoxic *B. coli* horse serum in 21 cases of indeterminate ulcerative colitis was presented (2.) The results were strikingly good, and, therefore, this type of serum therapy was continued until last year. All together, 41 cases were treated by the unconcentrated antitoxic serum. While the serum gave good results in 75 per cent of the cases, certain difficulties arose: (1) a number of batches of sera derived from several horses differed in ability to neutralize the *B. coli* against toxins of different strains of *B. coli*. Because only a small group of cases could be treated with each batch, exact evaluation of the effects was made less accurate than desirable; (2) the frequent necessity for introduction of large amounts of the unconcentrated serum intravenously sometimes led to shock and frequently to severe serum sickness; (3) the dilution of the serum in normal saline to offset these reactions brought about a loss and weakening of the antitoxic properties of the serum. In view of the encouragement gained from observations on this serum therapy, it seemed advisable to prepare a large single batch of concentrated antitoxic *B. coli* horse serum. Such a serum was then prepared in the Research Laboratories of Eli Lilly and Company using for immunization pooled strains of *B. coli* and their toxins obtained from the stools of patients with severe ulcerative colitis. A special attempt was made to include some strains from patients who were completely refractory to the previous unconcentrated serum therapy. The serum was then concentrated in the same laboratories, described by Mr. Jamieson in a personal communication, in the following manner:

To one volume of *B. coli* antiserum was added two volumes of distilled water. This was saturated with sodium chloride by the addition of the dry salt. The resulting precipitate was filtered off and discarded and the filtrate was then brought to 35 per cent saturation with ammonium sulphate. The resulting pre-

<sup>\*</sup>From the Medical Department and the Laboratories of The Mount Sinai Hospital, New York, N. Y.

precipitate was filtered off, pressed dry, and dialyzed for three days in the cold against running water. The dialyzed serum was then diluted sixteenfold with distilled water and subjected to isoelectric precipitation, using for adjustment dilute hydrochloric acid. After standing over night the precipitate was collected and dissolved in one per cent sodium chloride. The reaction was set at pH 6.9 to 7.1. "Merthiolate" (Sodium Ethyl Mercuri Thiosalicylate, Lilly) was added as a preservative, the final "Merthiolate" concentration being 1:10,000. The material was then Berkefeld filtered and tested for sterility and potency prior to release.

On retests in our laboratories the neutralizing potency of the serum ranged from 100 to 300 units per 1 cc. and from 600 to 1800 agglutinating and from 40 to 80 precipitating units.

*Method of Treatment:* The clinical use of the serum is described below: All patients were first studied for

ologic studies and the therapeutic test for amoebic infestation. Despite careful diet, vitamins, opium, transfusions, sulfanilamide or neoprontosil, antiseptic colonic irrigations and instillations, and liver extract, their course remained either uninfluenced or frequently downhill.

The analysis of the effect of the serum upon the patients was carried out in the manner described below:

I. The condition of the patient before the serum therapy was rated in a roughly quantitative manner by evaluating on a 10 per cent basis a number of factors, namely,

a. Fever; b. Number of stools; c. Sigmoidoscopic appearance; d. Radiography of the colon; e. General conditions; f. Toxemia; g. Subjective complaints; h. Weight changes.

II. *Evaluation of the effect of serum.*

The above factors were again each separately rated after the serum therapy on a basis of 10 per cent. The difference of the averages of the figures, described under I and II was taken as indicator of the degree of improvement obtained in each case. It should be pointed out that in the final evaluation the cases were grouped according to their severity, consideration being given to the fact that mild cases responded with greater improvement than the severe cases. Thus more credit was given to a definite improvement in a severe case than to a dramatic recovery of a mild case. For example, in cases 13 and 14 where the severity was rated as only 70 and 72, the serum effect was definitely 100 (excellent.) We decided, however, in these cases to rate the final result as "good" instead of "excellent."

*Final Results:* In all, 29 of the 35 cases treated were selected for the analysis. Six treated cases were not included. The reasons will be explained below. Of the 29 cases, 17 were severe and excellent results were obtained in 12 patients (70 per cent.) Of 7 moderately severe cases, 5 excellent and good results were seen. That is, 17 of the 24 moderately severe and severe cases showed good results; 20 were considerably benefited, 2 responded questionably and 7 patients failed to respond to the serum. Among the failures there were 2 deaths.

*Cases Excluded from the Analysis:* (1) F. V., male of 44 with severe colitis for 3 months. After intravenous serum, the temperature dropped to normal, the stools diminished to 1 or 2 daily, and he felt better. Because F. was a "right-sided" colitis, surgical therapy was instituted. He died of peritonitis due to a post-operative leak.

(2) H. D., boy of 23 with 6 weeks of severe ulcerative colitis. The first intravenous injection of serum was followed by a chill and sharp rise in temperature. It was decided not to continue serum therapy.

(3) A. R., girl of 22 with congenital polypoid of the colon complicated by an infectious mononucleosis like 6 weeks. After 20 cc. of serum intramuscularly there was a sharp chill. Her temperature then fell to normal. This case was not a colitis and, therefore, was not included in the series.

(4) E. C., man of 28 (Case No. 29 in Chart II) with a mild ulcerative colitis for 7 years, who was desperately sick for 10 weeks. Then he was delirious, toxic, pale, 160, incontinent rectally, edema of legs, and there was diffuse abdominal tenderness. He was practically moribund and ran high fever. After 150 cc. of the serum intra-

the presence of amoebic or bacillary dysentery. A course of emetine and carbarsone was given for 10 days in order to exclude amoebic infestation. Following this course, conjunctival and intradermal tests were performed with the serum diluted 1:10 and only patients showing no evidence of bacillary and amoebic dysentery and showing no reactions to the conjunctival and intradermal tests were selected for B. coli serum therapy. In one series of cases, 0.5 cc., 2 cc. and 5 cc. were given intramuscularly the first day at six hour intervals. If there were no severe reactions (chills, fever, urticaria), 25 cc. diluted with an equal volume of saline were slowly injected intravenously three times daily for two following days. In a second series of tests, 25 cc. of undiluted serum were given intramuscularly three times daily for a period of 2 days. In both series, approximately 150 cc. of serum was the average amount given. When early reactions were encountered or later serum sickness, adrenalin was administered.

*Clinical Material:* During the past two years, 35 cases of indeterminate ulcerative colitis have been treated (i.e., 15-intravenously, 19-intramuscularly, and 1-combined) with the Lilly concentrated antitoxic B. coli horse serum. The patients selected were all hospitalized and all chronically and seriously ill. Their course was characterized by fever, loss of weight, toxemia, abdominal pain, bloody and purulent diarrhea, anemia, and severe mucosal ulceration as revealed by sigmoidoscopy and radiographs. As already stated, a specific etiology was eliminated by bacteri-

CHART I

*Results of therapy with concentrated B. coli serum*

| Results      | Severe Cases Treated | Moderately-severe Cases Treated | Mild to Moderate Cases Treated | Total Cases Treated |
|--------------|----------------------|---------------------------------|--------------------------------|---------------------|
| Excellent    | 12                   | 3                               | 0                              | 15 (61%)            |
| Good         | 0                    | 2                               | 3                              | 5 (17%)             |
| Questionable | 1                    | 0                               | 1                              | 2 (7%)              |
| Failure      | 4                    | 2                               | 1                              | 7 (25%)             |
| Total Cases  | 17                   | 7                               | 5                              | 29                  |

muscularly, his temperature fell to normal; the stools dropped to 2 or 3 daily; and he gained considerable weight. The serum effect seemed almost miraculous. A mild colitis persisted. Several months later another severe attack supervened with delirium, fever, pellagra, and tetany. Ileostomy was refused and another 150 cc. of serum was given without effect. Two weeks later an acute perforation of the bowel occurred and he quickly succumbed. This case was not included in the series because the good effect of the first course of serum therapy was offset by the failure of the second course of treatment.

(5) F. W., a woman of 42 with two years of ulcerative colitis. A chill and sharp rise in temperature occurred after the first intravenous dose of 20 cc. of the serum. Its use was then discontinued.

(6) F. S., a woman of 77. She had had a mild ulcerative colitis for two months. An acute pneumonia then complicated her chronic bronchiectasis. During the pneumonia 78.5 cc. of the serum was given intramuscularly. Her pneumonia continued. Her death was apparently due to the pneumonia.

*Comparison of intravenous and intramuscular modes of administration of the concentrated B. coli serum:* Obviously, it would be advantageous to give the serum intramuscularly if the results were equally good. Immediate shock, dilution of the serum, and some technical difficulties involved in venipunctures, apparatus, etc., could be avoided. Actually, it was found that the intramuscular mode of administration of serum compared favorably with the intravenous route, thus 12 of 18 cases and 7 out of 10 cases, respectively, gave good results. We have, therefore, been using and advocating routine intramuscular administration of the undiluted concentrated serum.

*Serum Sickness:* Serum sickness was encountered in 15 of these 30 cases treated. It usually occurred as a single attack 5 to 7 days after the administration of the serum. The course was clearly mild. A localized erythema, somewhat elevated, over the area of the intramuscular injection and a mild diffuse urticaria lasting 1-3 days appeared as a rule. Arthritis, fever, nausea, and repeated attacks of urticaria were not seen. It was our impression that the serum sickness after intramuscular serotherapy was considerably less than after the intravenous route. Immediate serum shock of a mild nature (chill and fever) occurred very rarely (3 cases.)

*Repeated Administration of the Serum:* Since the disease has a striking tendency to recurrence it seemed important to determine whether the administration of the serum could be safely repeated during subsequent relapses of previously treated cases. This was attempted in 3 cases. In order to exclude an acquired sensitivity to horse serum, we repeated the conjunctival and intradermal tests. The patient's serum was studied for the presence of precipitins for horse serum. In one case (No. 29) the treatment was beneficial only the first time and remained without effect in the second treatment. In another instance (case 30), it was brilliantly successful in both attacks.

#### SUMMARY OF TYPICAL CASES ILLUSTRATING BENEFICIAL EFFECT OF THE SERUM THERAPY

Case 4. C. A., a young woman of 19 with a bloody diarrhea for 9 months and two weeks of high fever. On

admission to the hospital, she presented the picture of a desperately sick patient. Her temperature ranged from 101 to 105 daily with repeated chills. She had diffuse abdominal distension and tenderness. She was quite anemic (55%) and very toxic. There was no improvement despite three large transfusions. She was then given the serum, 72 cc. intravenously and 75 cc. intramuscularly. Two days thereafter her temperature fell and became normal in one week. Toxicity disappeared and the stools dropped from 7-10 daily to 1 semi-formed stool. Three weeks later sigmoidoscopy revealed a normal mucosa. She was seen five and twelve months after leaving the hospital. There was no evidence of colitis at these examinations. In the opinion of all those who made the observations the patient could be considered moribund on admission.

Case 11. M. R., a young man of 20. His disease ran a very severe course. He had bloody diarrhea, marked weight loss, and a high fever, 103-104 daily. The mucosa revealed superficial and also very deep ulcerations. The radiographs showed an advanced lesion of the entire colon and a perforative peritonitis was suspected. The patient appeared desperately ill, very toxic, and was considered a poor surgical risk for a proposed ileostomy. He was given 183 cc. of the serum intramuscularly. Twenty-four hours after the last administration of the serum, his temperature fell to normal by crisis. The bowel movements dropped from 8-10 daily to 1-2 stools which became formed. He gained 6½ pounds the week following the serum therapy. Twelve days later (after the last injection of the serum), his mucosa was normal sigmoidoscopically. He was seen again 10 months after leaving the hospital. He had gained 27 pounds, was in perfect health, and the mucosa was normal. It was the opinion of all observers that the result was brilliant.

Case 30. A. A., a young married woman of 21. She was ill for 9 weeks. The symptoms were high fever, bloody diarrhea, abdominal pain and tenderness, great loss of weight, anemia, and some delirium. She seemed very toxic. Sigmoidoscopy revealed a very severe ulceration of the colon. One hundred and twenty-two and five-tenths cc. of serum was administered intramuscularly. Three days later her temperature fell from 103°-104° F. to 101° F. and one week later it was normal. Her subjective state improved remarkably. Anorexia and vomiting changed to a ravenous appetite. The stools dropped from 7-8 to 1-2 daily and became formed. Two weeks after the serum administration the mucosa was completely healed. Within the next six months she gained 20 pounds and remained in perfect health. Following a period of excessive activity, late hours, travelling, and a gripe, there was a recurrence. The clinical picture was as severe as during the first attack. Since her conjunctival and intradermal tests for horse serum sensitiveness were negative and the blood revealed no precipitins for horse serum it seemed quite safe to administer the serum again. Again the same brilliant result was seen. The recovery was equally rapid and complete. She had gained weight rapidly and has remained well for a period of 7 months.

Case 20. G. R., an 8-year old boy (treated through the courtesy of Dr. Arthur Sohval.) This child had a severe bloody diarrhea for 1½ years. During the 2 weeks before admission to the hospital, his temperature rose to 105-106° F. daily. Despite sulfapyridine, neoprontosil, and repeated transfusions, he went downhill. On admission he was considered moribund by several consultants. Ileostomy was considered too dangerous. He was given 108 cc. of serum intramuscularly. Forty-eight hours later his temperature dropped to 101° F. It was normal on the sixth day. The stools dropped from 10-12 to 1-2 daily and became formed. Three weeks after the serum sigmoido-

scopy revealed a normal mucosa. Radiographs which during the height of his illness showed severe involvement of the entire colon, three months after the serum administration revealed a normal colonic outline with a small area of narrowing in the descending colon. The patient has gained a great deal of weight and with the exception of a slight trace of blood in the stool occasionally has remained in good health for the following 9 months up-to-date. He is now receiving B. coli vaccine therapy in an attempt to increase his resistance against a possible recurrence.

### COMMENT

It is necessary to emphasize again the difficulty of evaluating the therapeutic results in a disease characterized by spontaneous remissions and exacerbations. However, in our experience, the type of cases selected for serum therapy were those in whom the mortality expectation is ordinarily quite high. In one ten year period (1921-1931) in this hospital the mortality of the unoperated cases of indeterminate ulcerative colitis was 18 per cent.

When there is no lethal outcome, the disease is usually of long duration beset by complications and frequent surgical "interference."

It must be admitted that occasional excellent therapeutic results may be obtained with any one of a variety of therapeutic measures in a low percentage of cases, thus suggesting spontaneous remissions. It is only when a series of very sick cases whose illness is approximately of equal severity is treated by one measure and a striking and rapid subjective and objective improvement is seen in a high percentage of patients that one may be encouraged by the results. The latter requirement we believe has been met with the concentrated antitoxic B. coli serum-therapy of indeterminate ulcerative colitis.

Whether this form of passive immunity will lead to a permanent cure in the majority of cases cannot be answered as yet. Admittedly, the disease has a characteristic tendency to recur. It remains to be seen whether the addition of active immunization by vaccines and toxins of colitis strains of B. coli will help in the prevention of recurrences.

It may be emphasized again that no evidence exists to indicate that B. coli is the primary cause of the disease under consideration and the results obtained do not speak either for or against an assumption of the sort. We may, however, imply that the microorganism plays an important secondary role.

A final question arises whether the results may be at least in part attributed to a form of foreign protein shock-therapy induced by the foreign serum injections. In answer to this question the following facts are pertinent, namely: (1) good results were seen in most of the patients who did not experience chills or rises in temperature following the injections

(2) in a few cases in which 300 cc. of ordinary crude horse serum was administered there was no improvement, (3) we have not seen any striking results from the use of artificial hyperpyrexia, intravenous typhoid vaccine therapy, and the intravenous injections of antidysentery and antistreptococcus sera. Finally, it may be of some interest to mention the following experience.

Recently for a short period of time, no serum was available. During this time there were five rather severe colitis patients on the wards of this hospital. All patients received a course of emetine and carbarsone. One case made a brilliant recovery. In view of the fact that we have not seen any striking effect from the use of emetine and carbarsone in nonspecific ulcerative colitis, it seems fair to conclude that this particular case was an instance of amoebic colitis, although there were no amoebae found in the stool. Two cases went rapidly downhill, despite transfusions and neoprontosil, and died of perforative peritonitis. Two others were subjected to urgent ileostomy as a life-saving measure. While these 5 cases may not be representative of all the severe cases not treated with antitoxic B. coli serum, we have been impressed by the contrast in the clinical course of the two groups.

### SUMMARY AND CONCLUSIONS

1. Indeterminate ulcerative colitis is a disease in which B. coli may play an important pathogenic role as a secondary invader.

2. Whole and concentrated horse serum strongly antitoxic to B. coli has been prepared according to the principles of the Schwartzman Phenomenon.

3. The present communication deals with 29 new cases treated with concentrated antitoxic B. coli horse serum† which supplements a previous report dealing with 41 cases in a high percentage of which beneficial effects were obtained by means of the antitoxic whole horse serum.

4. Of the 29 cases described in this paper, 26 were greatly benefited; in two cases the results were questionable and the remaining 7 failed to show improvement.

5. In view of the encouraging results, the intramuscular use of concentrated antitoxic B. coli horse serum (Schwartzman) is advocated for treatment of severe and intractable cases of indeterminate ulcerative colitis.

### REFERENCES

1. Schwartzman, G.: Phenomenon of Local Tissue Reactivity and Its Immunological, Pathological and Clinical Significance. Paul B. Hoeber, Inc., Medical Book Department of Harper and Brothers, New York, 1937.
2. Schwartzman, G. and Winkelstein, A.: *Am. J. Dis. Child.* 55:2, 1931.

\*There were no thorough attempts to discover the amount in the intestinal mucosa as recommended for diagnosis of chronic infection.  
†This serum was prepared and concentrated in the research laboratory of Eli Lilly and Company.

# The Relationship Between Gastric Motility, Muscular Twitching During Sleep and Dreaming

By

H. B. McGLADE\*  
COLUMBUS, OHIO

IN 1922 Wada (1) made simultaneous records of hunger contractions and body movements during sleep. She reported that powerful contractions of the stomach were often associated with body movements and dreaming periods.

In 1936, while making a series of records of body movements during sleep in our laboratories, the writer became interested in a peculiar grouping of slight twitches of the right foot. These twitches began at the onset of sleep and occurred at 1.5 minute intervals over a period of 30 to 60 minutes. They appeared occasionally in three subjects out of twenty-five tested and in each case a definite dream could be remembered the following morning.

Although the usual time of the occurrence of foot twitches was between 11 p.m. and midnight, in one instance the group began at 1:15 a.m. and ended at 2 a.m. When the subject was questioned concerning his activities the evening before, he stated that he had eaten a banana at 10 p.m., one hour before retiring. This provided the first indication that food intake was related to the foot twitching and that the group of foot twitches indicated when the dreaming had occurred.

The experiments reported in this paper were performed on the three subjects whose sleep records showed the grouping of foot twitches and were designed to study the relationship between food intake, muscular twitching during sleep and dreaming. Evidence will be presented that the evacuation of the stomach accompanied the series of movements of the foot and the dreaming. It should be noted, however, that the synchronized recording of gastric motility and the twitching of the foot was impossible; the presence of a recording balloon at or near the pyloric sphincter prevented the occurrence of the foot twitches and of the dream regardless of the type of food eaten.

## EXPERIMENTAL PROCEDURE

A normal meal was eaten by each subject before 6:30 p.m., and no liquids were taken four and one-half hours before retiring at 11 p.m. Test food was eaten at variable times between 6:30 p.m. and 11 p.m. and the same food was not used on successive nights. The subjects on alternate nights slept on a coil spring bed, 30 inches wide and 72 inches long. All support was removed from 18 inches of the foot end of the springs at which point the free end of a Marey pneumograph was attached. A Marey tambour, smoked drum and a constant speed Harvard spring kymograph with a drum velocity of 31 mm. per hour completed the recording apparatus. A high degree of sensitivity

was maintained by introducing an air leak in the tambour rubber which allowed the recording lever to return to zero within five seconds following a change in body position.

Gastric motility was determined by means of a crystal microphone connected to a high-gain amplifier. The microphone, cushioned in sponge rubber, was strapped to the subject in a position directly over the pylorus. The sound associated with the relaxing sphincter had previously been determined under a fluoroscope by means of a stethoscope and barium sulfate. This sound changed quite rapidly as sleep approached. When the subject was awake the sphincter opened rather quietly and the sound of the partly digested food flowing into the duodenum faded slowly. However, during sleep with a test food in the stomach, the sphincter snapped open sharply and a rapid rumbling took place which faded out quickly (2.)

## RESULTS

Bananas, fresh pineapple, watermelon, etc., as set forth in Table I were effective in producing a group of foot twitches during sleep—always at approximately the same time interval after ingestion. The subjects ate the test food at 10 p.m., one hour before retiring and in each of these 59 experiments a group of foot twitches shown in Fig. 2 (C—Fig. 6) ended between 1:50 a.m. and 2:10 a.m. These results indicated a very close association between the time of ingestion of certain foods and the time of occurrence of the group of foot twitches. In order to further study this relationship the time of ingestion was varied.

On 10 occasions, 90 gm. of bananas were eaten by one subject at 6:30 p.m. following the evening meal. The group of foot twitches occurred immediately after the onset of sleep at 11 p.m. and ceased at about 11:30 p.m. as is shown in Fig. 1 (A—Fig. 6.) One subject on 5 occasions ate 90 gm. of bananas at 10:30 p.m. and a group of foot twitches occurred, ending at about 3:30 a.m., as shown in Fig. 3 (D—Fig. 6.) Another subject on 5 occasions ate 90 gm. of bananas at 10:45 p.m. Again in each case a group of foot twitches was recorded ending at about 6:30 a.m. as shown in Fig. 4 (E—Fig. 6.) On one occasion 90 gm. of bananas were ingested at 9 p.m. and a group of twitches ended at 1:10 a.m. (B—Fig. 6.) In each of the above cases the subject was awakened by means of an alarm clock at 7 a.m. and could clearly remember having dreamed. One subject on 3 occasions ate 90 gm. of bananas at 11 p.m., the time of retiring. In each case there was no twitching of the foot, nor dream remembered, during the night.

An association between gastric motility and the twitching of the foot during sleep was established by

\*Department of Physiology, The Ohio State University.  
Submitted August 1, 1941.





Fig. 1

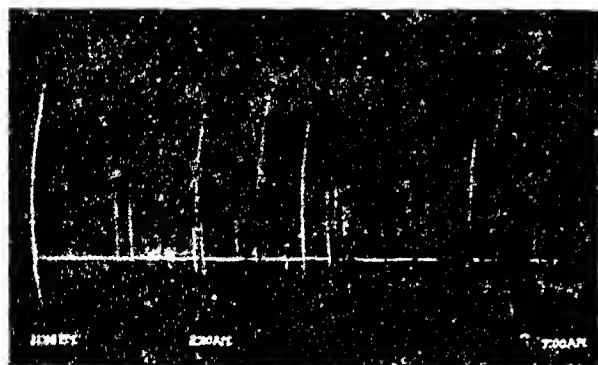


Fig. 2

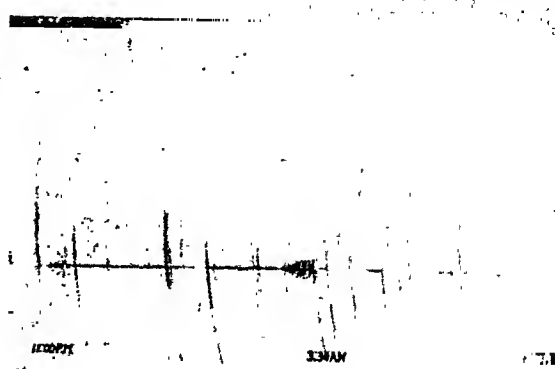


Fig. 3



Fig. 4

listening to the relaxing of the pyloric sphincter during 3 groups of foot movements. Following the procedure for Fig. 2 a microphone was placed over the pylorus before each subject retired. At the beginning of each sphincter relaxation (150 observations) a twitch of the right foot appeared.

Fig. 6 was obtained by plotting the average time for the ending of the groups of foot twitches as shown in Fig. 1 to 4 against the varied time of ingestion of the foods shown in Table I. This graph indicated that these foods, ingested at or very close

Figs. 1 to 4. Body movements during sleep. Groups of movements ending as indicated were controlled by the ingestion of bananas (90 gm.) at 6:30 p.m., 10 p.m., 10:30 p.m. and 10:45 p.m. respectively.

to the retiring period, remained in the stomach until after awakening occurred the next morning.

As previously stated, a dream was always remembered the morning following the appearance of each group of foot twitches. These dreams were never completed and always seemed to occur at the time of awakening. This appeared to be rather unusual so on

TABLE I

*The effect of the controlled ingestion of various foods\* on the twitching of the right foot during sleep.*

| Food                | Amount<br>gm. | No. of<br>Experiments | Ingestion<br>Time—p.m. | Foot Twitches<br>Began—a.m.** | Foot Twitches<br>Ended—a.m.** |
|---------------------|---------------|-----------------------|------------------------|-------------------------------|-------------------------------|
| Bananas             | 90            | 25                    | 10                     | 1:15                          | 2                             |
| Watermelon          | 360           | 8                     | 10                     | 1:15                          | 2                             |
| Fresh pineapple     | 90            | 10                    | 10                     | 1:15                          | 2                             |
| Cucumber            | 60            | 1                     | 10                     | 1:15                          | 2                             |
| Alfalfa             | 90            | 6                     | 10                     | 1:15                          | 2                             |
| Fresh green peppers | 60            | 3                     | 10                     | 1:15                          | 2                             |
| Cooked tomatoes     | 50            | 3                     | 10                     | 1:15                          | 2                             |
| Ice cream           | 240           | 6                     | 10                     | No foot twitches              |                               |
| Fresh tomatoes      | 50            | 5                     | 10                     | No foot twitches              |                               |
| Canned pineapple    | 90            | 4                     | 10                     | No foot twitches              |                               |

\*These foods were ingested by three subjects, one hour before retiring.  
Awakening occurred at 7 a.m.

\*\*Time was plus or minus 10 minutes.

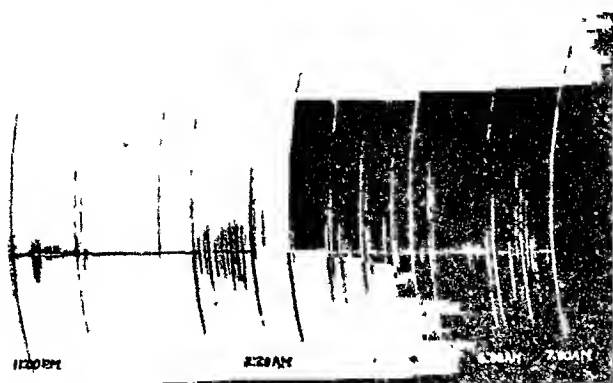


Fig. 5. Body movements during sleep. Groups of movements ending as indicated were controlled by the ingestion of peanuts at 11 p.m. and 2:20 a.m.

effort was made to determine the exact time the dream occurred.

The procedure for Fig. 2 was followed and 2 subjects, who had eaten different food, were awakened on 6 occasions by a gentle shaking at 1 a.m. before the group of foot twitches had begun. A dream could not be remembered, by either subject at this time. They were again awakened after the foot had started to twitch at about 1:30 a.m. In each case there was still no dream. When they were again awakened, after the first large body movement at the end of the group of foot twitches, they invariably stated that they had dreamed. The remainder of the night seemed to be free from further dreaming. These observations, made at a time unknown to the subjects, definitely placed the period of dreaming at the end of the group of foot twitches.

The results following the ingestion of one food, however, was found to be rather unusual. In 2 subjects on 4 occasions when 90 gm. of peanuts were ingested at 10 p.m., a group of foot twitches ended at 12:30 a.m. instead of the customary 2 a.m., as was true with other test foods. In one subject and on 3 occasions when ingested at the time of retiring (11 p.m.), 90 gm. of peanuts induced a group of foot twitches that ended at 2:20 a.m. The subject was immediately awakened and stated that he could remember having had a dream; ate 90 gm. more of peanuts and went back to sleep. Another group of foot twitches ended at 6 a.m., and when awakened at 7 a.m. by the alarm clock, another dream could be remembered. These results are shown in Fig. 5 and indicate that the stomach was emptied after the ingestion of peanuts sooner than after any other of the foods shown in Table I.

Any possible psychological origin of the groups of foot twitches and dreams that were caused to appear during these experiments seemed to have been discounted. For example, fresh pineapple had been quite effective in producing foot twitches and a dream response. One day it was impossible to obtain a fresh pineapple so canned pineapple was substituted. This was tried on 4 different nights with negative results. Only fresh pineapple proved effective. The same was true when fresh tomatoes were tried as a substitute for cooked ones. They did not induce foot twitches or dreams, yet they were eaten specifically for that purpose.

Therefore the type of food in the stomach prior to

retiring may determine whether or not a dream is to be experienced. Furthermore, the dream response appears at a definite time interval following food ingestion and follows the pyloric activity occurring during the emptying of the stomach. In these experiments the pyloric activity was accompanied by a characteristic series of foot twitches. Voluntary awakening never occurred at the completion of the group of twitches. In all experiments, when the subjects were awakened immediately following the completion of the group of twitches, a dream had been experienced and the remainder of the night passed without dreams unless additional food was consumed. It was unusual for a subject to remember more than 4 or 5 movements of any kind before going to sleep—suggesting that sleep occurred quite readily and that the subjects were under very little nervous tension.

Occasionally, some of these movements were twitches or jerks of the right foot synchronized with the relaxation of the pyloric sphincter. Coinciding with the first involuntary twitch prior to the onset of sleep was a sharp needle-like pain just below the ankle bone on the outer side of the foot. The pain occurred in lesser degree with the second twitch and thereafter failed to appear.

In all subjects, dreams were of the same general type, in that no bodily harm or painful sensation occurred to the dreamer. In one individual case 30 successive dreams caused by the ingestion of food were out-of-doors scenes in which the dreamer, usually accompanied by some other person, was the observer.

Twenty-five persons questioned stated that they believed that the reason a certain dream was never completed was because awakening occurred in the midst of the dream. This belief, while probably true in dreams involving actual pain or sensation, seemed to be entirely false in dreams elicited by the digestive system. In the experiments described in this paper the subjects were awakened in the morning, apparently in the midst of a dream, although the dream as such may have occurred 6 or 7 hours previously. This would indicate that the subjects were not aware of the passing of time during unbroken sleep.

It may be suggested that the bodily activity described in this paper was not present in more than 3

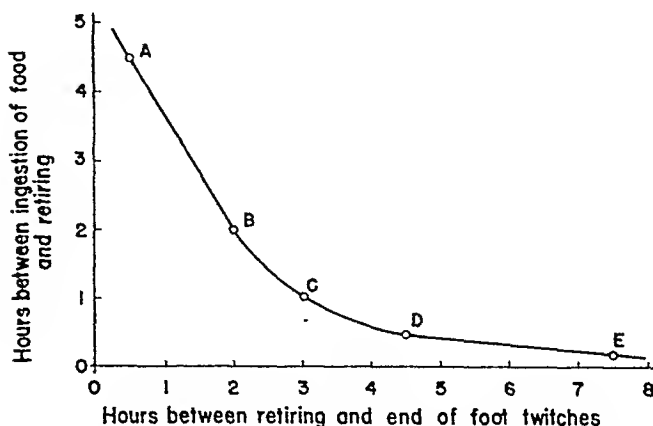


Fig. 6. Curve indicates the relationship between time of ingestion of specific foods and the groups of foot twitches during sleep (associated with pyloric activity and a dream.) Points on curve represent 80 experiments on 3 subjects.

out of 25 individuals because of differences in the degree of excitability of the nervous systems. The proper threshold must be reached in the brain during sleep to allow the stimulus associated with the relaxing sphincter to spread and involve a motor area.

### SUMMARY

In 3 persons (out of 25 tested) a group of 20 to 50 foot movements about 1.5 minutes apart ended 3 hours after the onset of sleep when certain foods were eaten one hour before going to bed. The relationship between these groups of movements and varied ingestion

times was predictable in all cases. Each foot movement was found to coincide with the sound of the relaxing pyloric sphincter. In the morning the subject remembered dreaming during the night. There is evidence that the dreaming occurred at the end of the series of movements and accompanied the complete evacuation of the stomach.

### REFERENCES

1. Wada, T.: Experimental Study of Hunger in Its Relation to Activity. *Arch. Psych.*, 5:1-65, 1922.
2. Hellebrandt, F. A., Tepper, R. H., Grant, H. and Catherine, R.: *Am. J. Dig. Dis. and Nutrit.*, 3:477-81, 1935.

## Proctoscopic Cinematography

By

J. F. PESSEL, JAY M. GARNER

and

J. F. NESSELROD

TRENTON, NEW JERSEY

**P**ICTURES of the normal recto-sigmoid and views of pathological variations were shown in colored stills and moving pictures. The examiner introduced a standard sigmoidoscope in the usual way and then attached a special photographic apparatus to it. As the picture is taken the operator moves the sigmoidoscope, at the same time observing the bowel through an attached periscope.

This type of cinematography is made possible by the use of coaxial lighting through a prism with a ribbon filament lamp and a condenser (1.) The beam from the condenser is reflected down one-half of the sigmoidoscopic tube and the image of the filament is focused on a point near the end of this tube. A correct color temperature is obtained by overloading the six volt lamp to eight volts while the exposures are being made.

The axis of the movie camera lens is in the other half of the sigmoidoscope, and in the extreme upper position of this axis is a periscope which obtains the image at the end of the barrel. This periscope has erecting prisms and gives a six fold magnification of the image.

A magazine movie camera is used because this type can be reloaded during the examination. A trigger lever starts the camera, increases the current to the lamp, and at the same time starts a motor which keeps the camera wound.

By means of the periscope mentioned above, the examiner is able to observe the bowel during the entire procedure thus decreasing the possibility of poor exposures very materially.

The first views shown were those of a normal bowel, observations of which began twenty-four cm. proximal and proceeded to the anus. Then followed in order views of rectal polyp, congenital polyposis, polypoid hyperplasia, adeno-carcinoma, chronic ulcerative colitis, chronic ulcerative colitis with secondary invasion by *Bacillus necrophorus*, tuberculous entero-

colitis, and melanosis coli. Movies of the X-rays of the colon of the congenital polyposis were inserted.

### PROCTOSCOPIC COLORED PHOTOGRAPHY

The stills are taken with another instrument similar to the one used for movies. This apparatus follows the same principals but uses a flash bulb for sufficient light to insure clearer detail. A slight modification of the regular sigmoidoscope was necessary.

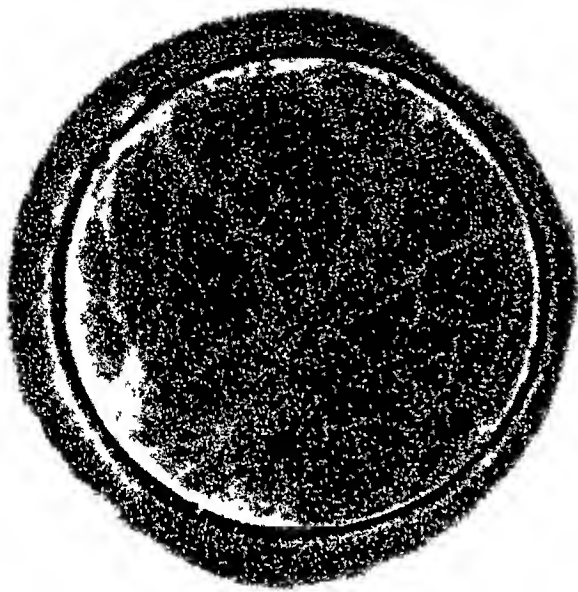
The first five stills were of normal bowel showing rectal mucosa with "chicken wire" vascular markings, valves, and sigmoidal mucosa with mucus. The next picture showed a pedunculated polyp the size of a cherry followed by one after fulguration. The eighth still was one of twelve or more sessile polyps in a case of congenital multiple polyposis with normal mucosa between. The ninth and tenth pictures showed adenocarcinoma of the rectum proven by biopsy. The latter shows interesting color variation between mucosa and the carcinoma. Numbers eleven and twelve were of idiopathic chronic ulcerative colitis. Then followed hyperplastic degeneration of the mucosa in chronic ulcerative disease. The last two were of tuberculous ulcers one of which was small, flat and the other deep and ragged type. The latter patient had chronic pulmonary and chronic laryngeal tuberculosis of long standing.

It is our belief that such color photography will become an indispensable aid in the teaching of an important diagnostic procedure to medical students and physicians. It will provide a means of obtaining permanent records for future reference. Finally, it will aid in the clarification of nomenclature by general exhibition and comparison.

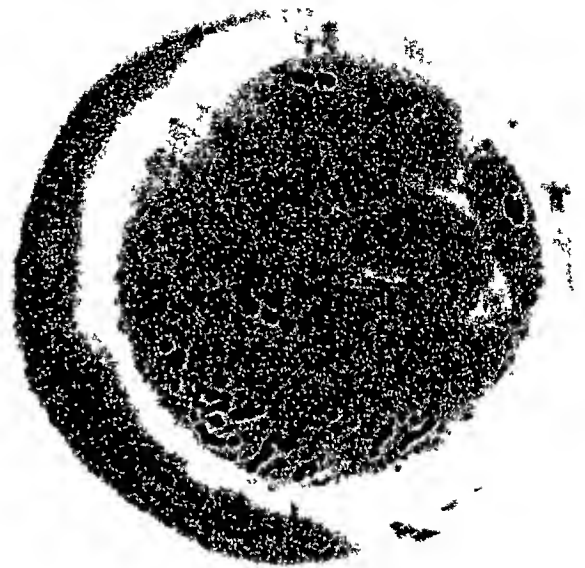
These pictures were taken in the clinics of the Evanston Hospital, Evanston, Illinois, the Chicago Tuberculosis Sanatorium and the Graduate Hospital, Philadelphia, Pa. (2.)

### REFERENCES

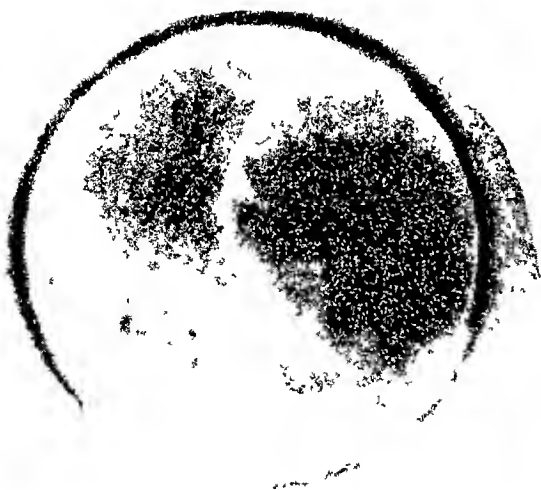
1. Brubaker, J. D.: *J. of Biological Photography*, 5:22-25, Dec., 1935.
2. Garner, J. M., Nesselrod, J. F. and Pessel, J.: *Proctoscopic Cinematography*, *Proc. Inst. of Rel. Chemo.*, 1937, May 11, 1941.



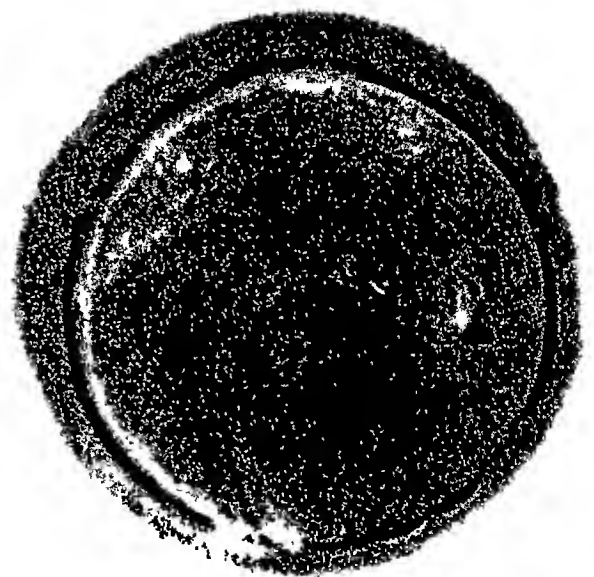
NORMAL MUCOSA



DIVERTICULUM OF THE SIGMOID



IDIOPATHIC ULCERATIVE COLITIS



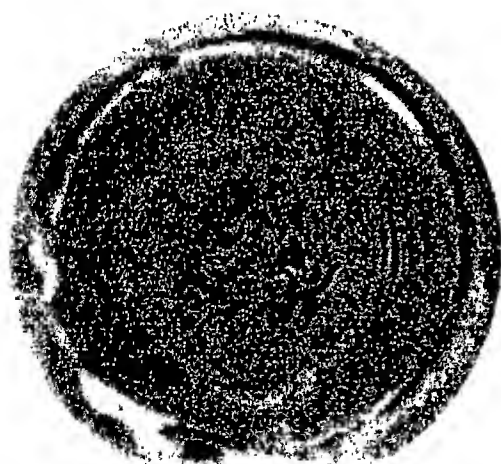
EARLY TUBERCULAR ULCERS



ADENOCARCINOMA OF RECTO-SIGMOID



MULTIPLE POLYPOSIS-CONGENITAL



SIMPLE POLYP



VENEREAL LYMPHOGRANULOMA

## The Significance of Dosage and Time Factors on the Value of the Bromsulphthalein Test for Liver Function\*

By

JOHN D. HELM, M.D.†  
and  
THOMAS E. MACHELLA, M.D.‡  
PHILADELPHIA, PENNSYLVANIA

THE technique originally described by Rosenthal and White (1) for testing the excretory function of the liver by means of an intravenously injected dose of bromsulphthalein has been modified so often that one frequently is at a loss to know what particular method to employ and also how to interpret the results from the various procedures. In an attempt to bring about a standardization of the technique and consequently greater confidence in it, we have compared in a selected group of subjects, including normals and some with hepatic disease, several of the suggested modifications. We have found that the collection of a single blood specimen 30 minutes after the intravenous injection of 5 mg. of the dye per kilogram of body weight constitutes an adequate test for ordinary clinical purposes.

### PROPOSED METHODS

The original technique consists in estimating, by comparison with suitable standards, the amount of dye retained in the blood stream at 5 and 30 minute intervals after the injection of 2 mg. of bromsulphthalein (in a 5 per cent solution) per kilogram of body weight. After securing a sample of blood from a vein in one arm, the dye is injected and then the two subsequent specimens at the proper time intervals are collected from the other arm for estimation of the contained dye. Normally, from 20 to 50 per cent of the dye is stated to be present in the circulating blood after 5 minutes, while all of it should have disappeared after 30 minutes.

The following modifications of this technique have been described. O'Leary et al (2) (1932) introduced the use of a test dose of 5 mg. per kilogram of body weight. In the series of subjects whom they regarded as controls, a retention of 0 to 8 per cent of the injected dye at the end of 30 minutes or of 0 to 4 per cent at the end of 60 minutes was accepted as normal. Shay and Schloss (3), Robertson et al (4) and Soffer (5) expressed the opinion that the 5 mg. dose was more sensitive and gave a higher percentage of positive results than the 2 mg. one. None of these investigators, however, compared the two methods in the same subject. Magath (6) used the 5 mg. dose and withdrew only one sample of blood 60 minutes after injection of the dye; he regarded a retention of more than 6 per cent as abnormal. Israel and Reinhold (7) employed the same dose, but measured the

dye concentration 30 minutes after injection. A retention of more than 6 per cent was considered abnormal. Rosenberg and Soskin (8) and Cates (9) also used the 5 mg. dose but accepted a retention of 0 to 10 per cent at the end of 30 minutes as within normal limits. Thus in the various reports, one finds a variation in the amount of dye injected, in the time intervals after which samples of blood are withdrawn and in the values which have been accepted as representing the normal. In an attempt to evaluate these factors we have compared the results when 2 and when a 5 mg. dose was administered in the same subject; also, the relative merits of taking the blood sample at 30 or at 60 minutes after the injection of the dye also were investigated.

Various other modifications of the test, which we have disregarded, have been proposed. MacDonald (10) made a rather extensive study of the rate of disappearance of the dye from the blood after injecting amounts varying from 2 to 10 mg. per kilogram of body weight. He withdrew specimens of blood every 5 minutes and plotted a curve of the rate of disappearance of the dye. Using the 2 mg. dose, he found the blood stream in the normal subject to be dye-free after 18 minutes, and, with the 5 mg. dose, after 25 minutes. White and his associates (11) retained the use of the 2 mg. dose, but withdrew 3 samples of blood within 15 minutes. They regarded as normal in adults a retention of 80 per cent at the end of 2, of 15 per cent at the end of 5, and of 5 per cent at the end of 15 minutes. Such methods, however, require considerable equipment and time and also are more or less disturbing to the patient. Furthermore, specimens of blood taken before one-half hour are apt to give dye readings too variable for proper interpretation (Shay and Schloss (3)), and the mixing of an injected dye with the blood stream is considered to be incomplete in less than 20 minutes (Sunderman and Austin (12.)) Consequently those modifications in which blood samples are withdrawn sooner than 30 minutes after injection have not been included in our comparisons.

### SUBJECTS AND PROCEDURE

A group of 50 adult patients with significantly enlarged livers or with a primary disease in which hepatic function was believed to be disturbed were selected from admissions to the medical wards of this hospital. The only other requisite was that the direct van den Bergh reaction of the serum be either negative or delayed, since a retention of the dye practically always occurs in patients whose serum gives either a

\*From the Gastro-Intestinal Section (Kinsey-Thomas Foundation) of the Medical Clinic, Hospital of the University of Pennsylvania.

†Edward W. Bok, Fellow and Senior Resident in Medicine, University of Pennsylvania Hospital, Philadelphia, Pa.

‡Fellow in Gastro-Enterology and Instructor in Medicine and in Physiology in the University of Pennsylvania Medical School, Philadelphia, Pa.

Submitted August 15, 1941.



biphasic or an immediate direct reaction. The tests, however, were performed in a series of 17 patients with a positive direct van den Bergh reaction, merely to obtain data to substantiate this point. In addition, twelve patients in whom no suspicion of hepatic disease had arisen were used as controls.

The tests were performed on successive days with the subjects fasting for 12 hours before each of them. Dye was injected intravenously in amounts of 2 and later of 5 mg. per kilogram of body weight and blood samples were taken at 30 and at 60 minute intervals after each injection. The same set of standards (Hynson, Westcott and Dunning, Baltimore), prepared according to Rosenthal's (1) recommendations for the 2 mg. dose, was used for each determination. When employed in estimating the retention of dye in the

serum after the 5 mg. dose, the reading was multiplied by 2.5. All the estimations were made by the same person. The direct van den Bergh reaction was determined in each instance prior to the dye tests, and the degree of bilirubinemia was determined either by the indirect van den Bergh reaction or by the coloring index.

### RESULTS

Thirty-eight of the 50 hepatic cases, on receiving the 5 mg. per kilogram dose, showed some retention of the dye after 30 minutes, and 27 of these even after 60 minutes. On receiving the 2 mg. dose, 21 of the 50 showed retention after 30 minutes, and only 3 of these after 60 minutes (Table I.)

Of the additional 17 patients, who gave either an immediate direct or a biphasic van den Bergh re-

TABLE I

The retention of dye in the serum of patients 30 and 60 minutes after injection of 2 and 5 mg. doses. The direct van den Bergh reaction in all cases is "negative or delayed"

| Case No. | Percentage Retention of Dye |         |               |         | Van den Bergh |                           |
|----------|-----------------------------|---------|---------------|---------|---------------|---------------------------|
|          | 5 mg. per Kg.               |         | 2 mg. per Kg. |         | Direct        | Indirect in sec. Per Cent |
|          | 30 Min.                     | 60 Min. | 30 Min.       | 60 Min. |               |                           |
| 1        | 0                           | 0       | 0             | 0       | negative      | 0.1                       |
| 2        | 0                           | 0       | 0             | 0       | "             | 0.1                       |
| 3        | 0                           | 0       | 0             | 0       | "             | 0.1                       |
| 4        | 0                           | 0       | 0             | 0       | "             | 0.1                       |
| 5        | 0                           | 0       | 0             | 0       | "             | 0.1                       |
| 6        | 0                           | 0       | 0             | 0       | delayed       | 0.2                       |
| 7        | 0                           | 0       | 0             | 0       | "             | 0.2                       |
| 8        | 0                           | 0       | 0             | 0       | "             | 0.4                       |
| 9        | 0                           | 0       | 0             | 0       | "             | 0.1                       |
| 10       | 0                           | 0       | 0             | 0       | "             | 0.45                      |
| 11       | 0                           | 0       | 0             | 0       | "             | 0.2                       |
| 12       | 0                           | 0       | 0             | 0       | "             | 0.45                      |
| 13       | 4                           | 0       | 0             | 0       | negative      | 0.1                       |
| 14       | 4                           | 0       | 0             | 0       | "             | 0.1                       |
| 15       | 4                           | 0       | 0             | 0       | delayed       | 0.1                       |
| 16       | 4                           | 0       | 0             | 0       | "             | 0.1                       |
| 17       | 1                           | 0       | 0             | 0       | negative      | 0.1                       |
| 18       | 4                           | 0       | 0             | 0       | "             | 0.1                       |
| 19       | 8                           | 0       | 0             | 0       | "             | 0.1                       |
| 20       | 12                          | 0       | 0             | 0       | "             | 0.1                       |
| 21       | 12                          | 0       | 0             | 0       | delayed       | 0.1                       |
| 22       | 12                          | 4       | 0             | 0       | "             | 0.1                       |
| 23       | 12                          | 6       | 0             | 0       | negative      | 0.1                       |
| 24       | 12                          | 4       | 0             | 0       | delayed       | 0.1                       |
| 25       | 12                          | 6       | 0             | 0       | "             | 0.1                       |
| 26       | 16                          | 12      | 0             | 0       | negative      | 0.1                       |
| 27       | 20                          | 0       | 0             | 0       | delayed       | 0.1                       |
| 28       | 20                          | 5       | 0             | 0       | "             | 0.1                       |
| 29       | 28                          | 8       | 0             | 0       | "             | 0.1                       |
| 30       | 8                           | 1       | 5             | 0       | negative      | 0.1                       |
| 31       | 12                          | 0       | 5             | 0       | delayed       | 0.1                       |
| 32       | 12                          | 4       | 5             | 0       | negative      | 0.1                       |
| 33       | 16                          | 4       | 5             | 0       | "             | 0.1                       |
| 34       | 16                          | 6       | 5             | 0       | "             | 0.1                       |
| 35       | 20                          | 8       | 5             | 0       | "             | 0.1                       |
| 36       | 20                          | 16      | 5             | 0       | delayed       | 0.1                       |
| 37       | 24                          | 24      | 5             | 0       | "             | 0.1                       |
| 38       | 16                          | 12      | 10            | 0       | "             | 0.1                       |
| 39       | 20                          | 4       | 10            | 0       | "             | 0.1                       |
| 40       | 24                          | 8       | 10            | 0       | negative      | 0.1                       |
| 41       | 24                          | 8       | 10            | 0       | "             | 0.1                       |
| 42       | 24                          | 8       | 10            | 0       | "             | 0.1                       |
| 43       | 24                          | 12      | 10            | 0       | delayed       | 0.1                       |
| 44       | 24                          | 8       | 10            | 0       | "             | 0.1                       |
| 45       | 28                          | 14      | 10            | 0       | negative      | 0.1                       |
| 46       | 24                          | 8       | 10            | 0       | "             | 0.1                       |
| 47       | 28                          | 12      | 10            | 0       | delayed       | 0.1                       |
| 48       | 32                          | 24      | 10            | 0       | "             | 0.1                       |
| 49       | 40                          | 12      | 20            | 5       | "             | 0.1                       |
| 50       | 44                          | 32      | 24            | 10      | "             | 0.1                       |

TABLE II

The retention of dye in patients in whom the direct van den Bergh reaction was "biphasic" or "immediate"

| Case No. | Van den Bergh |                          |               | Percentage Retention of Dye |         |               |         |
|----------|---------------|--------------------------|---------------|-----------------------------|---------|---------------|---------|
|          | Direct        | Indirect in mg. Per Cent | Icteric Index | 5 mg. per Kg.               |         | 2 mg. per Kg. |         |
|          |               |                          |               | 30 Min.                     | 60 Min. | 30 Min.       | 60 Min. |
| 1        | Biphasic      |                          | 10            | 0                           | 0       | 0             | 0       |
| 2        | "             |                          | 12            | 40                          | 0       | 0             | 0       |
| 3        | "             |                          | 12            | 12                          | 6       | 0             | 0       |
| 4        | "             |                          | 10            | 10                          | 20      | 10            | 0       |
| 5        | "             |                          | 16            | 36                          | 16      | 20            | 5       |
| 6        | "             |                          | 12            | 45                          | 30      | 30            | 10      |
| 7        | Immediate     | 0.5                      |               | 16                          | 8       | 0             | 0       |
| 8        | "             | 0.5                      |               | 24                          | 0       | 10            | 0       |
| 9        | "             | 0.5                      |               | 48                          | 28      | 35            | 10      |
| 10       | "             | 0.7                      |               | 40                          | 32      | 20            | 0       |
| 11       | "             | 0.85                     |               | 36                          | 4       | 20            | 0       |
| 12       | "             | 1.0                      |               | 20                          | 5       | 15            | 0       |
| 13       | "             | 1.1                      |               | 50                          | 36      | 5             | 0       |
| 14       | "             | 1.9                      |               | 64                          | 40      | 30            | 10      |
| 15       | "             | 2.9                      |               | 90                          | 60      | 80            | 40      |
| 16       | "             | 3.7                      |               | 70                          | 40      | 50            | 30      |
| 17       | "             | 1.8                      |               | 64                          | 44      | 40            | 20      |

action, 16 retained some of the dye for 30 minutes, and 14 for 60 minutes after the 5 mg. dose; while 13 showed retention for 30 minutes, and 7 for 60 minutes after the 2 mg. dose (Table II.)

None of the 12 controls showed retention at the 30 minute period, after either the 2 or the 5 mg. test dose.

#### COMMENT

These results indicate that a dose of 5 mg. of bromsulphthalein per kilogram of body weight and a single specimen of blood withdrawn after 30 minutes, as employed by Israel and Reinhold, offer a more satisfactory test than does the use of the smaller dosage or a longer time interval. It is simple to perform, requires little equipment and subjects the patient to only two venipunctures. It gives a sensitive and relatively reliable estimation of hepatic excretory ability. These results indicate that the 5 mg. dose is more sensitive in showing impaired hepatic function than the 2 mg. one, and that some patients, presumably with impaired hepatic excretion, are able to clear their blood stream completely of the dye within 60 minutes, even when the 5 mg. dose is employed.

That the use of the 5 mg. dose of the dye does not overtax the excretory ability of a supposedly normal liver is evidenced by the absence of its retention in our series of controls, as well as by the observations of MacDonald (10) in his normal subjects. Furthermore, 24 per cent of our cases, suspected of having hepatic disease, had no dye retention at the end of 30 minutes. Thus any dye retention 30 minutes after the injection of a dose of 5 mg. of bromsulphthalein per

kilogram of body weight may be considered as evidence of impaired hepatic excretory ability.

In the subjects with a biphasic or an immediate direct van den Bergh reaction, the dye was retained as expected. This type of van den Bergh reaction, as a matter of fact, in itself indicates impaired hepatic excretory ability, and in this respect at least the dye test is unnecessary. In such a patient, however, the dye test may furnish base-line information from which improvement may be judged after the jaundice has subsided.

#### CONCLUSIONS

1. The employment of a dose of 5 mg. of bromsulphthalein per kilogram of body weight yields a higher percentage of positive results than does that of a dose of 2 mg., and at the same time the larger dose does not overtax the excretory function of the liver.

2. The blood secured 30 minutes after the injection of the 5 mg. dose contains the dye more frequently than that secured after 60 minutes, and the 60-minute specimen adds nothing to the diagnostic value of the test.

3. The retention of any of the dye in the blood 30 minutes after the injection of a 5 mg. dose should be regarded as an indication of impaired hepatic excretion.

4. The technique, as used by Israel and Reinhold, that requires a 5 mg. dose of the dye and a single specimen of blood, secured after 30 minutes, may be regarded as the most satisfactory of the suggested modifications of the bromsulphthalein test.

#### REFERENCES

1. Rosenthal, S. M. and White, E. C.: Clinical Application of Bromsulphthalein Test for Hepatic Function. *J. A. M. A.*, 84:1112, 1925.
2. O'Leary, P. A., Greene, C. H. and Rowntree, L. C.: Diseases of the Liver: VIII. The Various Types of Syphilis of the Liver with Reference to Tests for Hepatic Function. *Arch. Int. Med.*, 44:155, 1929.
3. Shay, H. and Schloss, E. M.: Liver Function Tests in the Differential Diagnosis of Jaundice with Special Reference to the Galactose Tolerance Test. *Med. Clin. of N. Amer.*, 14:955, 1931.
4. Robertson, W. E., Swalm, W. R. and Kozelmann, F. W.: Functional Capacity of the Liver. *J. A. M. A.*, 90:2071, 1932.
5. Soffer, L. J.: Present Day Status of Liver Function Tests. *Medicine*, 14:185, 1935.
6. Magath, T. B.: The Takata-Ara Test of Liver Function. *Proc. Staff Meet. Mayo Clinic*, 10:493, July 3, 1935.
7. Israel, H. L. and Reinhold, J. G.: Detection of Cirrhosis and Other Diseases of the Liver by Laboratory Tests. *J. Lab. and Clin. Med.*, 23:558, 1938.
8. Rosenthal, S. M. and Sokol, S.: Azorubin S Test of Liver Function: Evaluation with Comparative Study of Bromsulphthalein and Hippuric Acid Tests. *Ann. Int. Med.*, 13:1644, 1940.
9. Cates, H. B.: Relation of Liver Function to Cirrhosis of Liver and to Alcoholism: Comparison of Results of Liver Function Tests with Degree of Organic Change in Cirrhosis of Liver and with Results of Such Tests in Persons with Alcoholism But Without Cirrhosis of Liver. *Arch. Int. Med.*, 67:383, 1941.
10. MacDonald, D.: Practical and Clinical Test for Liver Reserve. *S. G. O.*, 69:70, 1939.
11. White, F. W., Deutsch, E. and Maddock, S.: The Comparative Value of Serial Hippuric Acid Excretion, Total Cholesterol, Cholesterol Ester and Phospho Lipid Tests in Diseases of the Liver. *Am. J. Dig. Dis.*, 6:603, 1939.
12. Sunderman, F. W. and Austin, J. H.: The Measurement of Serum Volume. *A. J. Physiol.*, 117:474, 1936.

## The Treatment of Anorectal Infections With Suppositories Containing Sulfanilamide and Local Anesthetic: Preliminary Report\*

By

HAROLD LAUFMAN, M.D.

and

MORTIMER DIAMOND, M.D.

CHICAGO, ILLINOIS

THE increasing tendency toward the direct application of sulfonamide derivatives in the treatment of tissue infections and wounds has been stimulated by the undisputed proof of a local bactericidal action of these drugs when placed in direct contact with bacteria-laden tissue. This action is independent of any systemic effect (1). Furthermore, sulfanilamide is known to have an inhibitory effect on the growth of bacteria commonly found in human feces, such as *B. coli*, *streptococcus fecalis* and *streptococcus pyocyaneus* (2, 3, 4.)

In the light of such findings, it appeared that sulfanilamide in suppository form might be of some value in the local treatment of non-suppurative anorectal infections such as proctitis, cryptitis, papillitis, rectal ulceration, or the secondary local infections accompanying anal fissure, internal hemorrhoids, injuries and minor traumata to the anorectum.

It has been customary for most suppositories now on the market, to contain several soothing ingredients, an anodyne, an astringent, and perhaps one or two other medicaments. There is no doubt that such suppositories produce a local soothing effect. However, they do not directly attack the bacteria whose action is responsible for the inflammatory condition.

That sulfanilamide will have this action in the presence of constant re-contamination by feces, may be open to criticism. However, in the light of our experiences it is felt that the therapeutic value of sulfanilamide in suppositories cannot be denied. The purely local nature of the bactericidal effect of sulfanilamide in the rectum can be deduced from the findings of Turell, Marino and Nerb (5) who have shown that sulfanilamide incorporated in suppositories is poorly absorbed systemically from the isolated rectal pouch. We were unable to produce an appreciable sulfanilamide blood level in patients who used the suppositories three to six times daily for as long a period as three weeks.

There has been the belief among a certain number of proctologists that when rectal suppositories are inserted they do not remain implanted below the anorectal line, (level of internal sphincter) but probably find their way very shortly into the ampulla of the rectum, thus nullifying any purely local medicinal effect. The fact that marked relief from pain is obtained when suppositories containing a topical anesthetic are used in the treatment of painful lesions situated at or below the anorectal line, would seem to

adequately answer such assertions. Further, digital examination of the rectum even hours after the suppository has been inserted, will reveal the softened suppository in situ.

The base commonly employed in the manufacture of suppositories is cocoa butter. Its shortcomings are numerous. It must be refrigerated for storage, and if the suppository should have to be manipulated before proper insertion, the skin around the anus and the patient's fingers are covered with its grease. The objectionable qualities of cocoa butter have been largely overcome by the use of a water-soluble gelatin base.\* It has a melting point sufficiently high to permit storage without refrigeration. Its water-soluble quality allows rapid disintegration when brought into contact with the moisture of the rectum, and as urea intimate application of the jelly to the folds of the anorectal mucosa for a long period after insertion. Suppositories made with this base are easy to handle and are not greasy.

In order to adequately judge the therapeutic effect of sulfanilamide in suppositories, we used three types of suppositories. The first contained 1% sulfanilamide in a water-soluble base (designated Number 26); the second contained 1% sulfanilamide plus a topical anesthetic agent, gamma — (2-methylpiperidino) — propyl Benzoate hydrochloride, so-called Metycaine in a water-soluble base, (designated Number 27); and the third contained no medicaments, but consisted of the water-soluble base alone (designated Number 28). This latter suppository, the placebo, served a two-fold purpose. It served to show us the value of lubrication alone in the treatment of painful conditions of the anorectum, and also served as a control for the effects of the medications in the first two types of suppository.

The concentration of sulfanilamide was set at 1% because this strength has been shown to be non-injurious to the normal anorectal mucosa (5). The patients for this study were not selectively chosen but were taken consecutively as they presented themselves at the clinic and the office. The procedure of investigation was as follows: the patients were classified according to the anorectal pathology and then, in each group, alternate patients were given suppositories number 26, 27 and 28. This permitted a comparison of the effects of the various suppositories on any given pathologic entity.

The majority of cases were amenable to suppository therapy alone. However, some required other forms of treatment. In these latter instances suppositories

\*From the Proctological Division of the Sullow, Chase, Marshall, Green, Morgan, Brown Hospital and Mt. Sinai Hospital, Chicago, Ill.  
The suppositories used in this investigation were supplied by E. I. du Pont de Nemours and Company, Philadelphia, Indiana.  
Submitted Jan. 25, 1941.

\*Developed by Dr. Lally and Dr. Joseph, Indianapolis, Indiana.

therapy was not an attempt to supplant necessary surgical procedures but rather a complementary effort, and was used both pre- and post-operatively to reduce inflammation and to control symptoms. The reduction of the inflammation diminishes pain while reflexly the sphincter mechanism changes from the hypertonic to a more normal state. This further relieves the patient of his discomfort both during and between defecations. Some of this action is no doubt brought about by the factor of lubrication alone, which accounts for the degree of relief obtained in some patients by the use of glycerin suppositories or our placebo suppositories. A somewhat comparable palliation is accomplished by the oral or rectal administration of mineral oil, which softens the stool and diminishes its traumatic effect upon the anorectal mucosa and the sphincter. Low residue diets and increased fluid intake were prescribed for those patients whose stools were very hard.

We soon found that for practical purposes, the suppository containing sulfanilamide plus Metycaine (Number 27) not only gave rapid subjective relief, but gave the best end-results. Therefore, this report is concerned chiefly with those cases treated with this suppository.

One might raise the question as to whether the same results might not be obtained without suppositories of any kind, provided the regular forms of treatment were carried out. Our pessimism was expressed along this same line of thought until we were confronted with three facts: (1) Patients requested suppositories to use between visits to alleviate discomfort, pain and itching until their next visit. (2) When the suppositories were deliberately withheld, symptoms did not subside as rapidly, and proctoscopic findings showed a retardation in the progress of healing. (3) Patients who used suppositories for interval treatment were cured more rapidly than those who did not.

For the very mild cases, especially those of low grade cryptitis, it was often possible to bring about a cure with no treatment other than the use of suppositories. It is the practice of most proctologists to treat low grade anorectal infections by local applications of a mild antiseptic to the mucosa. It is therefore logical to expect that sulfanilamide applied to the inflamed mucosa several times per day in the form of a suppository, should have some curative effect.

## RESULTS

Thirty-one of forty-six unselected cases of various types of non-suppurative anorectal inflammations, were treated with suppositories containing sulfanilamide and Metycaine (Number 27) between visits. Of the remaining 15, six patients were given the control suppository containing no medication and nine received the suppository containing sulfanilamide alone. One case of pruritus (not based on any apparent local pathology), recovered after using the control suppository. Of the other patients who used the control suppository, aside from added lubrication, almost no relief was obtained and proctoscopic examination revealed practically no change in the appearance of the mucosa from one visit to another. All these patients noticed a radical reduction in local symptoms when Number 27 (sulfanilamide and Metycaine) was substituted for Number 26 (control), and examination of the mucosa showed rapid improvement.

Suppository Number 26 (sulfanilamide alone) was of some benefit in two cases of pruritus with a moderate degree of cryptitis. In two cases of severe cryptitis with symptoms of marked burning and constant desire to defecate, this suppository resulted in an almost complete cure within one and two weeks respectively. Insertion of the suppository gave no immediate relief, but as the cryptitis subsided, the itching and other symptoms gradually disappeared. The other four patients in which this suppository was used, complained that they had no subjective relief, although over a period of several days, the symptoms did subside gradually. However, when the suppository containing sulfanilamide plus Metycaine (Number 27), was substituted, these patients obtained rapid relief whenever the suppositories were inserted.

Our best results, then, were obtained with the suppository containing sulfanilamide and Metycaine (Number 27.) Of 31 patients treated with this suppository, proctoscopic examination revealed a complete cure in four weeks in 16 (51.6%). Partial cures were obtained in 15 patients (48.4%) within four weeks, and of these, five were completely cured after eight weeks. Thus, almost all cases in which this suppository was used, showed some beneficial effect upon the local disease.

Symptoms such as pain or burning were almost immediately relieved upon introduction of the suppository into the anus. Our criteria for relief from symptoms, however, were based upon whether this relief was sustained after discontinuance of the suppositories. On this basis, 26 or 83.9% experienced complete relief from symptoms within four weeks, while three or 9.6% were partially relieved and only two patients had no sustained relief within this period, although both had partial relief after six weeks and had to use suppositories only occasionally.

Other procedures were carried out in 16 patients (34.4%) of our series. These procedures consisted of 5% AgNO<sub>3</sub> cauterization for fissure in two cases; hemorrhoidectomy preceding the use of suppositories in three cases; hemorrhoidectomy after the use of suppositories in one case; sphincterotomy in two cases; excision of fissure and sphincterotomy in two cases; oral sulfanilamide for gonorrheal proctitis in one case, and X-ray treatment for pruritis in two cases. In every one of these cases there seemed to be a need for local palliation in the intervals between visits. This was obtained by the use of suppositories. In the remaining 30 cases, no local treatment was indicated other than the use of the suppositories, and a cure was obtained in each case. General measures consisted of mineral oil by mouth, increased fluid intake and low residue diet in those patients whose symptoms indicated the need for this regime.

The most striking observation in our series of cases was the rapid subsidence of the local inflammatory signs. It has been our experience in the past that despite the symptomatic relief afforded by suppositories or other measures, the signs of mucosal and sub-mucosal inflammation, as observed proctoscopically, cleared up very slowly, or not at all. In other words, the local changes subsided much more slowly than the symptoms. When suppositories containing sulfanilamide plus Metycaine (Number 27) were used as a

supplement to necessary rectal procedures, cures were obtained in a higher proportion of cases and within a shorter period of time than has been our experience with other measures.

### SUMMARY AND CONCLUSIONS

Suppository medication conveniently and effectively provides prolonged treatment in various non-suppurative anorectal inflammatory processes. In many instances in this series of cases it was curative, while in those cases requiring surgical procedures, it was complementary, aiding recovery by reducing inflammation and inducing symptomatic relief. The most favorable results were obtained with suppositories containing 1% sulfanilamide plus a local anesthetic, gamma — (2-methylpiperidino) — propyl Benzoate

hydrochloride, so-called Metycaine, in a water-soluble gelatin base. This is a preliminary report; further investigation is being continued. We are also investigating the therapeutic value of suppositories containing 5% sulfathiazole and Metycaine.

### REFERENCES

1. Fuller, A. T., Colebrook, L. and Maxted, W. R.: The Mode of Action of Sulfanilamide. *J. Path. and Bact.*, 51:105, July, 1940.
2. Ravdin, I. S., Rhoads, J. E. and Lockwood, J. S.: The Use of Sulfanilamide in the Treatment of Peritonitis Associated with Appendicitis. *Ann. Surg.*, 111:53, Jan., 1940.
3. Rosenburg, S. and Wall, N. M.: The Treatment of Diffuse Peritonitis by the Direct Intraperitoneal Introduction of Sulfanilamide. *S. G. O.*, 72:568, March, 1941.
4. Laufman, H. and Wilson, C. E.: Some Experimental Observations on the Prophylactic Intraperitoneal Introduction of Crystalline Sulfanilamide. *Arch. Surg.*, 44:55-59, Jan., 1942.
5. Turell, R., Marino, A. W. M. and Nerb, L.: Studies on the Absorption of Sulfanilamide from the Large Intestine. *Ann. Surg.*, 112:117, 1940.

## The American Gastroscopic Club

The first annual meeting of "The American Gastroscopic Club" will be held on Sunday, June 7, 1942, at 9:30 a.m. in Atlantic City, Hotel Claridge, Binnacle Room.

All members of the profession, especially gastroenterologists, internists and surgeons are invited to attend and to participate in the general discussion.

### PROGRAM

*Symposium on Symptomatology of Chronic Gastritis with Special Reference to the Conditions in the Army and Navy*

- 9:30 Meeting comes to order  
Report of Secretary
- 9:40 Rudolf Schindler, Chicago: Introduction—On chronic epigastric distress and on the anatomic foundation of chronic gastritis
- 10:30 Crawford F. Barnett, Atlanta: Gastroscopic and clinical symptoms of chronic superficial-atrophic gastritis
- 10:50 Edward B. Benedict, Boston: Gastroscopic and clinical symptoms of chronic hypertrophic gastritis

- 11:10 George B. Eusterman, Rochester: (by invitation) Clinical significance of chronic gastritis
- 11:45 Seymour Gray, Chicago: Epigastric symptoms in alcoholics with and without gastritis
- 12:00 John Tilden Howard, Baltimore: Gastroscopic findings in cholecystectomized patients

### LUNCH

- 1:30 Col. John L. Kantor, New York: (by invitation) Significance of chronic dyspepsia for the Army in World War I.
- 2:05 Capt. Rubin Gold, Santa Barbara: Gastroscopic findings in chronic dyspepsia in the Army
- 2:25 Capt. Frank McGlone, Denver: Incidence of gastritis in draftees, soldiers and war veterans
- 2:40 General discussion to be opened by James B. Carey of Minneapolis
- Alterations of the program due to the war situation may become necessary.

Joseph B. Kirsner, M.D.,  
Secretary-Treasurer.

## Abstracts of Current Literature

FRANKLIN HOLLANDER, Associate Editor in Charge of Abstracts, New York, N. Y.

ALBERT CORNELL, New York, N. Y.  
MAURICE FELDMAN, Baltimore, Md.  
CHARLES A. FLOOD, New York, N. Y.  
M. H. F. FRIEDMAN, Philadelphia, Pa.  
J. DUFFY HANCOCK, Louisville, Ky.  
THOMAS A. JOHNSON, Philadelphia, Pa.  
ALLEN A. JONES, Buffalo, N. Y.  
N. W. JONES, Portland, Ore.  
HENRY H. LERNER, Boston, Mass.  
PHILLIP LEVITSKY, Montreal, Can.

JESSIE LOVE, Louisville, Ky.  
FRANZ J. LUST, New York, N. Y.  
IRA A. MANVILLE, Portland, Ore.  
ARTHUR E. MEYER, Brooklyn, N. Y.  
FRANCIS MURPHY, Milwaukee, Wis.  
H. NECHES, Chicago, Ill.  
FRANK NEUWELT, Gary, Indiana  
SAM OVERSTREET, Louisville, Ky.  
J. F. PESSEL, Trenton, N. J.  
DAVID J. SANDWEISS, Detroit, Mich.

RUDOLPH SCHINDLER, Chicago, Ill.  
MICHAEL SHUTKIN, Milwaukee, Wis.  
VIRGIL E. SIMPSON, Louisville, Ky.  
H. J. SIMS, Denver, Colo.  
HENRY TUMEN, Philadelphia, Pa.  
ROBERT TURELL, New York, N. Y.  
EDGAR WAYBURN, San Francisco, Calif.  
JOHN WILLARD, Philadelphia, Pa.  
C. WILMER WIRTS, Philadelphia, Pa.

[Microfilm copies of papers may be obtained from Medicofilm Service of the Army Medical Library at 25c for each complete article, not exceeding 25 pages in length—and 10c for each additional 10 pages or fraction thereof. Prepayment is not requested. Remittance may be made with subsequent orders and in such manner as found most convenient. Address—Medicofilm Service, Army Medical Library, Washington, D. C.]

### CLINICAL MEDICINE MOUTH AND ESOPHAGUS

TOUROFF, ARTHUR S.: Perforation of the Cervical Esophagus with the Flexible Gastroscope. *Ann. Surg.*, 114:369, Sept., 1941.

"An unusual case of accidental perforation of the cervical portion of the esophagus with the flexible gastrocope, is presented. The rubber bougie, which constitutes the distal portion of the instrument, became detached and

remained lodged in the neck after the gastroscope was withdrawn. The diagnosis of free perforation of the esophagus was made clinically, and confirmed by immediate roentgenologic examination, which disclosed a large quantity of air in the soft tissues of the neck and the missing bougie lying free in the periesophageal tissues at the root of the neck. Prompt operation was performed through an external approach, the foreign body removed, and the perforation cared for. Recovery was uneventful.

# Familial Occurrence of Chronic Ulcerative Colitis (Thrombo-Ulcerative Colitis): Report of Cases

By

RAYMOND J. JACKMAN, M.D.

and

J. ARNOLD BARGEN, M.D.†

ROCHESTER, MINNESOTA

THE question of communicability of the streptococcal form of chronic ulcerative colitis is raised frequently. Members of a family who live in close contact with the patient naturally are concerned about whether or not they may contract the disease. It is a pertinent and justifiable question, as the disease has many points in common with tuberculosis. Then, too, there are still a few investigators who confuse thrombo-ulcerative colitis with a late stage of an infection by the *Shigella paradysenteriae* group of organisms. Bacillary dysentery usually occurs in localized outbreaks in which many members of a community or family are afflicted. If the aforementioned theory is subscribed to, then it should be presumed that the familial incidence of the disease would be relatively great. However, most available evidence points to the view that the disease is caused by infection with specific micro-organisms, of which streptococci are at least important.

In our experience, the incidence of the disease in several members of a family is rare, but the aforementioned queries prompted us to study a series of cases of this type which have come under our observation.

This report deals with a group of cases in which two or more members of the same family were found to have the disease. Occasionally, patients have related that a member of the family had had "colitis" or "bowel trouble," but in most instances data were not available to substantiate the belief that other members of the family had ulcerative colitis. Consequently, only those cases in which the disease was observed at the Mayo Clinic are reported here. The following report of cases is presented in family groups rather than patients for the obvious purpose of comparing the mode of onset, course of the disease and living habits. Only data pertinent to the questions of communicability and familial tendency are included.

In a review of the records of 900 cases, it was found that in seventeen (1.8 per cent), two or more members of a family had the disease. These seventeen patients came from seven families.

## REPORT OF CASES

*Family 1.* Two brothers, whose ages were eleven and sixteen years, respectively, registered at the Mayo Clinic in October, 1935. The disease of both patients became evident at the same time (almost to the day), sixteen months prior to registration at the clinic. The onset was insidious and none of the usual predisposing factors could be elicited in either case. Both patients had lived on a

farm all of their lives, in the same household; the three other members of the family had never had any complaints referable to the bowel.

From the insidious onset the disease had run a moderately severe course and interestingly enough, the degree of severity and the extent of involvement of the disease, as determined by proctoscopic examination and by roentgenologic studies of the colon, were almost identical. Diplostreptococci were cultured from the bowel of each patient; results of agglutination studies for the various types of *Shigella* organisms were negative. The response to treatment was similar and satisfactory, and in a communication from them in the latter part of 1939 they stated that they had not had any subjective evidence of the disease for a year.

*Comment.* The identical nature of the disease, even to the extent of the same day of onset is interesting and naturally gives rise to several unanswerable questions as far as our present knowledge of chronic ulcerative colitis is concerned. Although three other members of the same household were not afflicted, these brothers had shared the same bed and their living habits had been similar. Two cases such as these might lead one to believe in the infectious nature of the disease.

*Family 2.* Two brothers, whose ages were nineteen and twenty-two years, respectively, registered at the clinic on April 16, 1940. The disease of the younger brother began insidiously six years prior to registration at the clinic, when he was thirteen years of age. The disease had progressed relentlessly and in 1936, ileostomy had been performed elsewhere. Proctoscopic examination revealed the lumen of the bowel to be contracted to about 1.5 cm. in diameter. At 12 cm. above the dentate margin the lumen of the bowel was about 5 mm. in diameter.

The disease of the older brother did not become evident until about eight months before his registration at the clinic, or about five and a half years after the onset of the younger brother's disease. During this five and a half years these boys had lived together, even to the extent of sleeping in the same bed. The older brother had been working as much as sixteen hours a day, and although the onset of the disease had been insidious, during the course of this time it was of a much more severe nature than that of the younger brother. Proctoscopic examination revealed the usual picture and roentgenologic studies revealed involvement of the entire colon in both cases. The course of the disease had been severe and was far advanced on initial examination at the clinic. Three other members of the family did not have intestinal trouble of any kind.

*Comment.* The most striking factor in the cases of these brothers seemed to be the interval of five and a half years between the time of onset and the relative severity of the disease.

*Family 3.* Three members of this family, a sister aged twenty-two years and two brothers aged twenty-five and

\*Section on Proctology, Mayo Clinic.  
†Division of Medicine, Mayo Clinic.  
Submitted September 19, 1941.



twenty-two years, respectively, were examined at the clinic. It was stated that one other brother, who had never been examined at the clinic, had a similar condition, and that still another brother had died of the disease. The parents, four other brothers and three sisters never had had any symptoms referable to the bowel. This family lived in a rural town in the Middle West. The dates of onset of the intestinal disease were widely separated. The sister had had symptoms for five years prior to her first visit to the clinic in 1922. We were informed that she died in 1930, after ileostomy had been performed elsewhere.

The next member of this family examined by us was the brother, twenty-five years of age, who registered at the clinic in November, 1934. Symptoms of the disease had been present for three years. We were informed of this patient's death in 1937.

The brother, twenty-two years of age, was examined at the clinic in December, 1934. He related that he had had bloody diarrhea for two years. In a recent communication he stated that he had rather frequent, moderately severe exacerbations of the disease. The diplostreptococcus of colitis was cultured from the rectal lining in the case of the brothers. Cultures were not made in the case of the sister.

**Comment.** Here again, the most striking feature of the disease in this family group was the similarity of its course, that is, a severe process which ended fatally for three of the members, two of whom were examined at the clinic.

**Family 4.** Two brothers, thirty-two and thirty years of age, respectively, had had symptoms of an inflammatory disease of the bowel which had begun insidiously about a year prior to registration at the clinic. No significant predisposing factors were elicited. Both had a regional type of ulcerative colitis (group 2), in which the ascending and transverse portions of the colon were involved.

**Family 5.** The first member of this family, a woman eighteen years of age, was first examined at the clinic in 1915. The onset of her disease when she was at the age of eleven, was fulminating in character and had followed measles. The progress of the disease was relentless and death occurred at the age of thirty-four years.

Her brother, thirty-four years of age, was first examined at the clinic in 1933. His trouble had begun insidiously after the removal of several infected teeth, two years prior to registration. Subsequent removal of two more teeth caused a severe flare-up of the disease.

**Family 6.** The patient, a woman forty years of age, registered at the clinic in June, 1934. She had had symptoms of chronic ulcerative colitis for a year. Proctoscopic examination revealed the usual picture and roentgenologic studies, moderately active involvement of the entire colon by the disease. The diplostreptococcus of colitis was cultured from the rectal lining. Response to treatment was extremely satisfactory.

In February, 1941, the woman brought her son, aged fifteen years, who had had symptoms for five months, to the clinic. In July he was still in the hospital under treatment. The mother had been free of intestinal symptoms for more than two years; proctoscopic examination revealed a scarred but healed mucous membrane.

In both cases the onset of the disease was insidious without apparent predisposing factors. The son was an only child. Both patients were extremely ill during the course of the disease.

**Comment.** When more than one member of a family is afflicted with chronic ulcerative colitis, an unusual opportunity is afforded for comparison of the nature of the disease as to onset and course. The most striking feature of these two patients was the similarity of the course of their disease.

**Family 7.** Two sisters, aged forty-one and thirty-nine years, respectively, registered at the clinic in 1939. The onset of symptoms of both patients was insidious, and became evident on the same day, and presumably after the sudden death of their father, a year prior to registration. At that time, the two sisters and their mother had gone to a spa for a rest. Both the sisters previously had had constipation and after drinking the water at the springs, began to have loose stools. The older sister's trouble began with the passage of a little blood in each stool and then in the course of a month there would be an occasional gush of clotted blood without stool. She also passed a great deal of blood with every stool, and at the date of her first visit to the clinic in November, 1939, she was so depleted and exsanguinated that it was impossible to carry out either proctoscopic or roentgenologic examinations. In spite of repeated transfusions and many other supportive measures, she died as a result of massive hemorrhage eleven days after admission to the hospital. Necropsy disclosed chronic ulcerative colitis which involved the entire colon.

The disease of the younger sister was relatively mild, with little bleeding and only four to six semiformal stools mixed with blood daily. Fear, worry or nervousness always aggravated her symptoms markedly.

At this writing, the mother who partook of the waters at the springs, two brothers and three other sisters are at their home in Canada, are living and well. They have not had any symptoms of intestinal disease.

**Family 8.** A woman, fifty years of age, registered at the clinic in January, 1941, and gave a history of chronic ulcerative colitis. She stated that her daughter had similar symptoms. The patient's symptoms had begun five years prior to registration in an insidious manner without any apparent predisposing factors. The disease had run a fairly mild course. Response to treatment was satisfactory. Roentgenologic studies of the colon disclosed involvement throughout its entire extent.

In May, 1941, the patient returned to the clinic with a daughter eighteen years of age. The daughter's symptoms had begun six months prior to registration at the clinic, or about five years after onset of her mother's disease. The daughter's colitis had begun in a fulminating manner after a severe cold which affected the lungs. After the initial violent attack of colitis, her symptoms had been relatively mild.

The diplostreptococcus of colitis was isolated from the rectal lesions of both patients. The patients occasionally had slept in the same bed. The daughter's disease became evident five years after the mother's. The entire colon was involved in both instances but both had relatively mild trouble when examined. Two other children, whose ages were twenty-two and fourteen years, respectively, lived at home with the patients and never had had any symptoms of intestinal disease.

#### COMMENT

This series of seventeen patients observed at the Mayo Clinic and two other members of one family in whose cases presumptive diagnosis of ulcerative colitis was made provides interesting food for thought. The number is small, although similar instances have been reported by Crohn, P. W. Brown and others. The actual incidence of the occurrence of the disease in more than one member of a family in only 1.8 per cent of a group of 900 cases makes us hesitate to place any significance on its familial occurrence. However, the similarity of onset and course of the disease of some members of a family, together with its actual onset at the same time in several, tends to lay stress at least on its infectious nature. Further, the relation of onset after removal of infected teeth in one case lends stress

to this. Also the presence of the disease in five members of one family tends to support its infectious nature. Two sets of brothers who slept together contracted the disease. If the fact is considered that in two cases the disease began after severe grief, we are inclined to think that infection plus proper soil are important.

Finally, the wholly dissimilar onset and course in several cases raise the question if the occurrence of the disease among several members of the same family is not purely coincidental. At any rate, we do not have enough evidence to speak of its contagious nature. We might go further and say that its rare occurrence argues strongly against it.

## The Gastric Mucosa in Benign Adenomas

By

RUDOLF SCHINDLER, M.D.<sup>1</sup>

CHICAGO, ILLINOIS

**H**AS the inflamed gastric mucosa a greater tendency to develop tumors than the normal one? Does especially the so-called "atrophic gastritis"† predispose to tumor formation? This frequent condition consists microscopically (1, 6) of thinning of the gastric mucosa, of reduction and even disappearance of the gastric glands, of cellular inflammatory infiltration and of metaplasia of the epithelium; it is characterized gastroscopically by thinning and greenish-grey discoloration of the mucosa and by the appearance of blood vessels (5.)

It is well-known that older pathologists and, in recent times, especially Saltzman (4) and Konjetzny (3) have advanced the theory that gastric carcinoma develops on the soil of chronic gastritis. It is not easy, however, to prove this theory. The chronic gastritis found at autopsy may have developed secondarily to the carcinoma. There are cases in which no definite gastritis can be seen. In fact, in 10 of 50 cases of gastric carcinoma studied by me (to be published elsewhere) the gastric mucosa appeared normal gastroscopically and microscopically.

The question whether or not benign epithelial tumors are more prone to develop in an atrophic than in a normal mucosa can be answered more readily. It would be difficult to understand how a pea-sized adenomatous polyp covered by intact mucosa should cause atrophic gastritis. If both conditions are found together, this might either be a coincidence, in which case the incidence of adenomatous polyps should be the same in a normal and an atrophic mucosa; or the atrophic gastritis predisposes to the development of adenomatous polyps: in this case one should expect to find polyps relatively more frequently with an atrophic than with a normal mucosa. It will be shown in the following analysis that the second assumption is the correct one, that is, adenomatous polyps are more prone to develop on the soil of atrophic gastritis than in a normal gastric mucosa. The only objection against the following analysis could be that in the case of polyps microscopic examination is rare and the interpretation of the gastroscopic picture may be doubtful. This objection is, in my judgment, not valid. In the many cases of gastric carcinoma (to be published elsewhere) in which gastritis was seen gastroscopically,

and in which microscopic examination became possible, severe unequivocal gastritis was invariably found at the microscopic examination. On the other hand, in most cases of carcinoma with a gastroscopically normal mucosa no sign of inflammation or atrophy was discovered microscopically. However, a few mistakes were made: mild proliferation of the surface epithelium was missed gastroscopically in two cases, and in one case severe atrophic gastritis was overlooked. Therefore, in the following gastroscopic study, if an error has been made, it would probably be in favor of the occurrence of normal mucosa together with adenomatous polyp. Such a mistake, if corrected, could obviously only serve to emphasize the final result of the analysis.

In a total of 2,167 patients examined gastroscopically 36 adenomatous polyps were observed. Cases of

TABLE I

|                    | All Patients | Uncomplicated Atrophic Gastritis | P.A. |
|--------------------|--------------|----------------------------------|------|
| Number of cases    | 2167         | 310                              | 43   |
| Number of adenomas | 36           | 15                               | 6    |
| Percentage         | 1.65%        | 4.8%                             | 14%  |

evidently inflammatory pseudopolyps and one case of hyperplastic polyps (7) have not been included in this series. Thus benign adenomatous polyp was found in 1.65% of all patients gastroscopied.

In 10 of these 36 cases the mucosa appeared to be normal. In 26 cases a definite gastritis was seen. In 21 cases this gastritis was atrophic in character; in 2 cases the diagnosis of superficial gastritis and in 3 cases that of hypertrophic gastritis was made.

Among the total of 2,167 patients were 310 cases of uncomplicated atrophic gastritis; 15 or 4.8% of these patients had benign adenomatous polyps. In addition to the 310 patients with uncomplicated atrophic gastritis there were 43 patients suffering from pernicious anemia. In this disease, the atrophic gastritis usually is severe and wide-spread. In 6 or 14% of these 43 patients adenomatous polyps were found (see Table I.)

<sup>1</sup>From the Frank Billings Medical Clinic, Department of Medicine The University of Chicago

<sup>†</sup>Chester Jones (2) prefers the expression "gastric atrophy." I believe this condition is an inflammation, but I will not discuss this question here.

Submitted September 15, 1941.

The comparison becomes more impressive if we take out the cases with atrophic gastritis from the total sum of cases (see Table II.) In 1,814 patients

TABLE II

|                    | Patients Without Atrophic Gastritis | Patients With Atrophic Gastritis |
|--------------------|-------------------------------------|----------------------------------|
| Number of cases    | 1,814                               | 353                              |
| Number of adenomas | 15                                  | 21                               |
| Percentage         | 0.83%                               | 6%                               |

who did not have atrophic gastritis only 15 adenomatous polyps—0.83%—were found; whereas 21 of 353 patients with atrophic gastritis had adenomatous polyps—6%. In the second group benign adenomatous

polyps occurred seven times more frequently than in the first one.

## CONCLUSION

Gastroscopic observations of 36 cases of benign gastric adenomatous polyps leads to the conclusion that atrophic gastritis has a seven times greater predisposition to the formation of such tumors than has the normal gastric mucosa. However, 15 of 36 patients with adenomatous gastric polyps did not have an atrophic gastritis as seen gastroscopically.

## REFERENCES

1. Faber, Knud.: Gastritis and Its Consequences. *Oxford Press*, 1935.
2. Jones, Chester N.: Clinical Evaluation of Gastritis. *Am. J. Dig. Dis.*, 8:205, 1941.
3. Konietzky, G. E. and Magenkrebs, D.: Stuttgart. F. Enke, 1938.
4. Saltzman, Frederick: Studien über Magenkrebs mit besonderer Berücksichtigung d. Schleimhautveränderungen. *Arch. A. D. patholog. Inst. d. Univ. Helsingfors*. Jena: G. Fischer, p. 335, 1913.
5. Schindler, H.: Gastroscopy: The Endoscopic Study of Gastric Pathology. The University of Chicago Press, Chicago, 1937.
6. Schindler, R. and Murphy, H. M.: Symptomatology of Chronic Atrophic Gastritis. *Am. J. Dig. Dis.*, 7:7, 1940.
7. Schindler, R. and McGlone, F.: Familial Occurrence of Hyperplastic Gastric Polyps. *Arch. Surg.*, 41:1483, 1940.

## Bleeding Peptic Ulcer\*

## A Clinical Study with Special Reference to the Meulengracht Regimen

By

N. W. CHAIKIN, M.D.†

and

OSCAR TANNENBAUM, M.D.‡

NEW YORK, NEW YORK

THERE have been admitted to the wards of the Metropolitan Hospital of New York City, 744 cases of peptic ulcer (e.g., gastric, duodenal and marginal.) Hemorrhage occurred in 101 cases with 114 admissions. In eighty-six cases the treatment was only medical, and in fifteen cases it was surgical. The surgical cases will not be discussed here. The present paper is limited to a study of patients with: (1) gross hematemesis, (2) visible melena, (3) signs of shock, (4) a falling or a very low blood pressure, (5) marked anemia and (6) syncope. Mild cases which presented simply occult blood in the stools or those with a doubtful diagnosis were not included in this series.

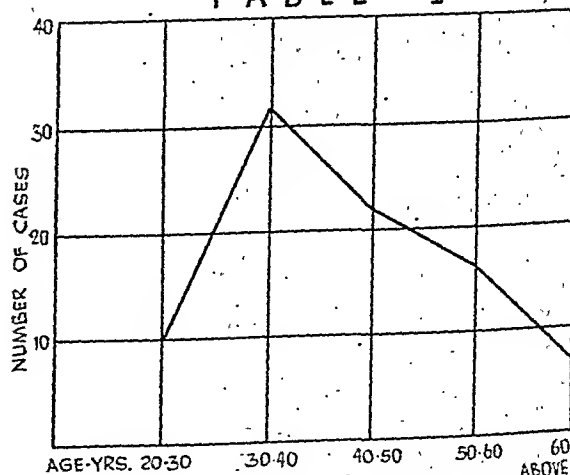
There were 82 white patients and four colored ones in this study. The youngest patient was twenty-two years of age and the oldest sixty-five. The incidence according to age is shown in Table I. Evidently bleeding from peptic ulcer is predominantly a disease of the middle-aged patients, a fact that other observers have noted (Goldman (1) and Crohn (2.))

In relation to sex, hemorrhage occurred in seventy-eight males and eight females, a ratio of 9.5 to 1 for the entire group. The distribution as to type of ulcer is as follows: duodenal, sixty-six cases; gastric, twelve cases; marginal, six cases, and combined duodenal and gastric, two cases.

## TREATMENT

We have compared the old starvation regimen with the new Meulengracht method of treatment. Up to 1937 the treatment of gastro-intestinal hemorrhage in the wards of the Metropolitan Hospital was that of starvation with transfusion, the giving of fluids parenterally, and alkalis by mouth. There were fifty-six cases treated with this method with a mortality of 6.9 per cent. On the other hand, thirty cases treated with the Meulengracht diet and supportive measures since 1937 resulted in one death, and this was due to

TABLE I



\*From the New York Medical College, Metropolitan Hospital, Department of Medicine, Linn J. Boyd, Director, Roy Upham, Chief of Section in Gastro-Enterology.

†Instructor in Gastro-Enterology, New York Medical College, Associate Visiting Physician Metropolitan Hospital.

‡Assistant Clinical Visiting Physician Metropolitan Hospital.  
Submitted August 5, 1941.

perforation and not hemorrhage. Assuming that this patient's death was caused by the hemorrhage, which is very doubtful, the mortality appears to have been reduced to less than one-half of what it was with the older method of treatment.

In addition to the lowering of the mortality by means of the Meulengracht diet, there was a decided shortening in the number of days of hospitalization. The starved patients spent on an average of thirty-eight hospital days as compared with twenty-eight days for the patients treated with the Meulengracht regimen.

The routine treatment of bleeding peptic ulcer in the wards of the Metropolitan Hospital is now: (1) small frequent transfusions and sedatives in the presence of shock; (2) the immediate institution of the Meulengracht diet; (3) the giving of parenteral fluids in the presence of dehydration, and (4) the administration of alkalis, antispasmodics, iron and vitamins.

## SUMMARY

(1) In 744 cases of peptic ulcer studied, bleeding occurred in 101 cases, an incidence of 13 per cent.

(2) In eighty-six cases of bleeding peptic ulcer the treatment was medical, and in fifteen cases it was surgical. The surgical cases are not considered in this study.

(3) The peak of incidence of bleeding peptic ulcer occurred in the third and fourth decades.

(4) There were fifty-six cases of bleeding ulcer in which the patient was treated by supportive measures and starvation with a mortality of 6.9 per cent. In the case of thirty patients receiving the Meulengracht regimen there was one death from a perforation. The feeding treatment appears then to have lowered the mortality. It also shortened the average stay in the hospital from thirty-eight to twenty-eight days.

## REFERENCES

1. Goldman, L.: *J. A. M. A.*, 107:1537, 1936
2. Crohn B. B. and Lerner H.: *Am. J. Dig. Dis.*, 6:15 1939.

# Investigation of the Relationship Between Blood Sugar and General Complaints Following Subtotal Gastric Resection\*

By

A. SCHWARTZ, M.D., I. REINGOLD, M.D.

and

H. NECHELES, M.D., Ph.D.

CHICAGO, ILLINOIS

IT has been known for a long time, that a small group of patients following subtotal gastric resections, may complain of nausea, epigastric discomfort, weakness, dizziness, perspiration, palpitation, and fatigue following a meal. These complaints last a variable length of time, usually a half hour, and slowly disappear. Sometimes it is necessary for the patient to lie down following a meal to obtain relief, or even to ingest small quantities of food while lying down. It was thought that these complaints were due to a hypoglycemia as the result of a more rapid emptying time of the stomach and a more rapid absorption of glucose in the intestines, of a disturbance of the vegetative nervous system, or of a combination of these factors. Recently Glaessner (1) reported that the complaints were not due to a hypoglycemia, but to a hyperglycemia, the hypoglycemia being a "secondary effect" and of no importance in relation to the symptoms. In our experience, we have associated symptoms of distress following a meal with distension of the remainder of the stomach, and particularly of the duodenum and jejunum (2.) In view of these opposed interpretations we considered this problem worthy of further investigation.

Many patients treated for peptic ulcers, or following operations for ulcers, have a low plasma Vitamin C level. It has been assumed that this is the result of a dietary deficiency. Whether a low plasma Vitamin C content plays a part in the production of the general

complaints of patients following subtotal gastrectomy has not been determined. For this reason, we attempted to find a relationship between the plasma Vitamin C level, the sugar tolerance curve (3) and the general complaints of patients following subtotal gastric resections.

## METHODS

Sucrose tolerance tests and Vitamin C determinations were performed on 14 patients following subtotal gastric resections with posterior gastrojejunostomies, and on one patient (15) with a posterior gastrojejunostomy. 100 grams of sucrose in a glass of orange juice was given to each patient who had fasted the previous nine hours, except one who had taken alkaline powders and milk before the test (6.) The patients drank the solution while sitting in a chair, in order to simulate normal conditions. Sucrose was the sugar of choice because of its abundant use in every day life. Four blood samples were drawn from each patient: a fasting sample, another fifteen minutes after ingestion, the third one hour after ingestion, and the last sample two hours after the ingestion of the test solution; blood sugar determinations were made by the Somogyi method.

Plasma Vitamin C was determined by the method of Farmer and Abt (4), on fasting blood samples, the normal lower limit being 0.75 mg. %.

## RESULTS

Patient 1, a 50 year old female, was operated in 1930 for a duodenal ulcer. She complained of a lack

\*From the Departments of Gastro-Intestinal Research and Surgery, Michael Reese Hospital.

\*Aided by the Nelson Morris Fund  
Submitted April 15, 1941

of appetite for the past four months. She had been taking five to six small meals daily, and never had symptoms suggestive of hypoglycemia. Fifteen minutes following ingestion of the sucrose solution, she complained of nausea. At this time the blood sugar was 137 mg. %, obviously not a hyperglycemia level. The nausea which lasted four or five minutes was not present at the end of one hour when the blood sugar rose to 337 mg. %, or at the end of 2 hours when the

blood sugar was 87 mg. %. The nausea apparently was not due to a hypoglycemia or a hyperglycemia, but to a distension of the duodenum or jejunum, or to the effects of a concentrated solution on a more or less inflamed gastric mucosa.

Patient 2, a 40 year old male, was operated in 1936 for a gastric ulcer. For the past several months he had been complaining of nausea and sweating, and of a sensation of warmth following a full meal, which

TABLE I  
*Oral sucrose tolerance tests in patients with subtotal gastric resections*

| Patient |     |     | Cause for Subtotal Resection  | Time Interval Since Resection | Present Complaints                                      | Blood Sugars in mg. % |         |       |        | Complaints During Test                                    |  |                         |
|---------|-----|-----|---|-------------------------------|---|-----------------------|---------|-------|--------|---|--|-------------------------|
| No.     | Age | Sex |   |                               |   | Fasting               | 15 Min. | 1 Hr. | 2 Hrs. | Time (Min.) After Injection                               | Complaints   | Plasma Vitamin C, mg. % |
| 1       | 50  | F   | Duodenal ulcer  | 11 years                      | Lack of appetite — 4 months                             | 85                    | 137     | 337   | 87     | 15  | Nausea lasting few min.                                  | 1.67                    |
| 2       | 40  | M   | Gastric ulcer   | 5 years                       | Nausea, warmth, sweating after full meal lasting ½ hour | 95                    | 138     | 208   | 99     | 30  | Sensation of warmth and dizziness, lasting few minutes   | 0.75                    |
| 3       | 45  | M   | Duodenal ulcer with pyloric obstruction   | 14 days                       | None  | 96                    | 153     | 185   | 165    | —   | None   | 0.43                    |
| 4       | 30  | M   | Duodenal ulcer  | 6 months                      | Headaches and dizziness not related to meals            | 77                    | 133     | 182   | 42     | 15  | Sensation of warmth, headache, lasting ½ hour            | 0.415                   |
| 5       | 56  | M   | Duodenal ulcer  | 4 months                      | None  | 92                    | 118     | 178   | 100    | —   | None   | 0.39                    |
| 6       | 48  | M   | Bleeding duodenal ulcer   | 5 months                      | None  | 112                   | 162     | 167   | 127    | (had fast and powders before test) None                   |  | 1.44                    |
| 7       | 51  | M   | Non-patent gastro-enterostomy stoma; duodenal ulcer                               | 12 days                       | None  | 82                    | 123     | 167   | 115    | 35  | Nausea for 5 minutes                                     | 0.42                    |
| 8       | 45  | M   | Duodenal ulcer with pyloric obstruction   | 12 days                       | None  | 91                    | 167     | 158   | 129    | —   | None   | 0.46                    |
| 9       | 68  | M   | Duodenal ulcers   | 7 years                       | Epigastric pain 1 hr. p.c. relieved by alkali           | 92                    | 142     | 135   | 73     | Epigastric pain before test was relieved by test solution |  | 0.67                    |
| 10      | 47  | M   | Duodenal ulcer  | 4 years                       | None  | 84                    | 115     | 122   | 100    | —   | None   | 0.775                   |
| 11      | 60  | M   | Duodenal ulcer  | 11 years                      | None  | 80                    | 130     | 154   | 55     | 20  | Sensation of warmth and mild dizziness lasting 5 minutes | 1.10                    |
| 12      | 53  | F   | Duodenal ulcer  | 13 days                       | None  | 76                    | 122     | 143   | 113    | 5   | Slight nausea lasting few minutes                        | 0.399                   |
| 13      | 56  | M   | Duodenal ulcer  | 14 days                       | None  | 98                    | 78      | 97    | 132    | —   | None   | 1.170                   |
| 14      | 41  | M   | Bleeding duodenal ulcer   | 14 days                       | None  | 80                    | 137     | 103   | 62     | —   | None   | 0.42                    |
| 15      | 54  | M   | Closure of gastric perforated ulcer and gastrojejunostomy for pyloric obstruction | 9 months                      | Epigastric pain after meals (jejunal ulcer)             | 75                    | 125     | 182   | 53     | —   | None   | 0.42                    |

lasted about one-half hour. He stated he often had to lie down to obtain relief. Thirty minutes following the ingestion of the test solution, he complained of nausea, and of a sensation of warmth and dizziness, lasting about ten minutes, which was relieved on lying down. At the end of one hour, when the patient had a blood sugar of 208 mg.  $\%$ , he had no complaints. Obviously, the complaints were not connected with the high blood sugar of 208 mg.  $\%$ .

Patient 3, a 48 year old male, was operated for a duodenal ulcer and a pyloric obstruction 14 days before the test. He had no complaints before or during the test, although the blood sugar rose to 185 mg.  $\%$  one hour after the ingestion of the test solution.

Patient 4, who was operated for a duodenal ulcer 6 months before the test, complained of headaches and dizziness, on and off, for 3 months, apparently not related to meals. He developed a headache and a sensation of warmth fifteen minutes following the ingestion of the test solution, which lasted 45 minutes. The symptoms had disappeared when the blood sugar was at its peak (182 mgm.  $\%$ ), and did not return at the rather low level of 42 mg.  $\%$  at the end of 2 hours. His complaints, apparently, had nothing to do with the level of the blood sugar.

Patients 5 and 6 had no complaints during the test, although patient 5 had a blood sugar of 178 mg.  $\%$  at the end of one hour, a level at which hyperglycemic shock takes place, according to Glaessner.

Patient 7, a 51 year old male was operated in 1922 for a pyloric obstruction, at which time a gastro-enterostomy was performed. He entered Michael Reese Hospital in May, 1941, complaining of vomiting and epigastric pain. Twelve days following a subtotal gastric resection (a non-patent gastro-enterostomy stoma and a duodenal ulcer were found), he was subjected to the test. Thirty-five minutes after the ingestion of the sugar solution, he complained of nausea lasting five minutes. His blood sugar levels, however, remained within normal limits.

Patients 8, 9 and 10 presented nothing outstanding as far as complaints and blood sugar levels were concerned.

Patient 11, a 60 year old male, was operated for a duodenal ulcer in 1930. Twenty minutes following the ingestion of the test solution, he complained of a sensation of warmth and dizziness which lasted for five minutes. No complaints were present at the end of two hours when the blood sugar was 55 mg.  $\%$ .

Patient 12, a 53 year old female had been operated for a duodenal-ulcer 13 days before the test. She complained of nausea 5 minutes after the ingestion of the test solution, lasting for a few minutes. Again, no hyperglycemic or hypoglycemic blood sugar levels were present at the time of the complaints.

Patient 13, a 56 year old male, had no complaints during the test, although he had a low blood sugar curve.

Patient 14, a 41 year old male, was operated for a bleeding duodenal ulcer 14 days before the test. He responded with a level of 62 mg.  $\%$  two hours after the ingestion of the test solution, but he had no complaints.

Patient 15, a 54 year old male, had a gastro-jejunosomy performed for a pyloric obstruction 9 months before the test. He was admitted to Michael Reese Hospital complaining of epigastric pain after

meals and had an area of epigastric tenderness. A diagnosis of a jejunal ulcer was made. He was tested after he had been in the hospital 10 days, and had been on a regimen of milk-cream and alkali, and was free of complaints. His blood sugar after one hour was 182 and after two hours, 53 mg.  $\%$ . Nevertheless, no hyperglycemic and hypoglycemic symptoms had occurred.

## DISCUSSION

From our observations, we are unable to find any correlation between the complaints of patients having gastric resections, such as, fullness after meals, nausea, sweating, and flushing, and the level of their blood sugar response to a sucrose test meal. Dibold (5), and Lapp and Dibold (6) believed that these complaints were due to a hypoglycemia, as the result of a disturbance in vagus activity. Beckerman (7) believed that faster emptying of the stomach, increased permeability of the mucosa of the upper small intestines, and gastro-intestinal and hepato-pancreatic reflexes, accounted for the hyperglycemia and subsequent hypoglycemia. Koranyi (8) reported that post-operative hypoglycemia is related to a mechanical disturbance of the vegetative nervous system by regional anesthesia or by operative interference. Glaessner (1), on the other hand, stated that the post-operative complaints were the result of a hyperglycemia, and not of a hypoglycemia. He passed a duodenal tube into the jejunum, injected a solution containing 100 grams of sugar in 250 cc. of water, and performed blood sugar determinations at regular intervals. He found that after 10 minutes the majority of his patients had various complaints, namely, nausea, vomiting, palpitations, and trembling, which he correlated with high blood sugar levels. He did not take into consideration the fact, that the duodenum and jejunum at this time were probably at the maximum of distension. Hurst (9) found that a feeling of fullness after beginning to eat may arise if the upper small intestine is distended by food going through a gastro-enterostomy opening. Alvarez (10) observed the same following jejunal feeding. Ivy (11) passed a balloon into the duodenum of human subjects and distended it; symptoms of nausea, pain, dizziness, faintness and uneasiness appeared.

Our results indicate that the complaints of patients following gastric resections are apparently the result of a distension of the duodenum and jejunum. Nausea, warmth, dizziness and headaches appeared in a number of patients between 5 and 35 minutes after the ingestion of the test solution. These complaints lasted a varying length of time, from a few to 45 minutes. At no time were we able to correlate the symptoms with a hyperglycemia, (Patients 1, 2, 3, 4, 5), or with a hypoglycemia (Patients 4, 11, 14, 15.)

The majority of our blood sugar curves confirm the finding of Beckerman, Dibold and Koranyi of a rapid, steep rise and a sudden fall. The rapid rise may be explained by a rapid emptying of the stomach and a subsequent rapid absorption by the intestinal mucosa, and the hypoglycemic level by the theory of Soskin (12), who accounts for it by the decrease in the supply of sugar by the liver to the blood, in response to the influx of exogenous sugar.

We have also observed that the symptoms in our patients could be alleviated by lying down after each



meal (as has been reported by other authors: Alvarez (13), Walters (14) and may be prevented by the taking of small feedings at frequent intervals. In cases of gastritis or jejunitis proper therapy has to be instituted.

We were unable to find any relationship between the plasma Vitamin C, the complaints, and the sugar tolerance tests.

### SUMMARY

1. Fourteen patients having undergone subtotal gastric resections and 1 patient with a gastrojejunostomy

were subjected to an oral sucrose tolerance test.

2. No relation was found between the blood sugar level and the complaints of dizziness, warmth, perspiration, palpitation and nausea.

3. We believe that the above complaints were due to a distension of the upper small intestine, which can be prevented by the taking of frequent small meals, or relieved by lying down after a meal.

4. No relation between the plasma-Vitamin C level and blood sugar levels or with the above symptoms was observed.

### REFERENCES

1. Glaessner, C. L.: *Arch. des mal. de l'app. Dig.*, 22, 1939, and in English translation: *Hyperglycemic Shock. The Review of Gastro-Enterology*, Vol. 7, p. 528, Nov.-Dec., 1910.
2. Strauss, A. A., Strauss, S., Levitsky, P., Scheman, L., Seidman, E. E., Arens, R. A., Meyer, J. and Necheles, H.: *Physiological and Clinical Study of Patients After Subtotal Gastrectomy. Am. J. Dig. Dis. and Nutr.*, Vol. IV, No. 1, March, 1937.
3. Sigal, A. and King, C. G.: Influence of Vitamin C Deficiency Upon Resistance of Guinea Pigs to Diphtheria Toxin. *Glucose Tolerance. J. Pharm. and Exper. Therap.*, 61:1-9, 1937.
4. Farmer, C. J. and Alt, A. F.: Ascorbic Acid Content of Blood. *Proc. Soc. Exper. Biol. and Med.*, 32:1625, June, 1935.
5. Dibold, H.: Disturbed Nutrition Following Gastric Resection. *Med. Klin.*, 29:1138, 1933.
6. Lapp, F. W. and Dibold, H.: Blood Sugar Curves and Gastric Resections. *Klin. Woch.*, Vol. 12:517, 1933.
7. Beckerman, F.: Spontaneous Hypoglycemia Following Gastric Operations. *Dtsch. Med. Woch.*, 59:683, 1933.
8. Koranyi, A.: Spontaneous Hypoglycemia Following Operations on the Stomach. *Deutsches Arch. fur Klinische Medizin*, Vol. 173, p. 333, 1936.
9. Harat, A. F.: *The Sensibility of the Alimentary Canal*. London, p. 22-28, 1911. Cited by Alvarez, p. 251.
10. Alvarez, W. C.: *Introduction to Gastro-Enterology*, 3rd. ed., Paul B. Hoeber, Inc., N. Y., 1910.
11. Ivy, A. C.: A Brief Review of the Physiology of the Duodenum. *Radiology*, July, 1927.
12. Soekin, S. and Allweis, D.: Hypoglycemic Phase of the Dextrose Tolerance Curve. *Am. J. Physiol.*, Vol. 110, p. 4-7, 1934.
13. Reference 10, p. 507.
14. Walters, W., Lewis, E. B. and Lemon, R. G.: Primary Partial Gastrectomy (Polya Type) for Duodenal Ulcer. *S. G. O.*, Vol. 71, p. 240-243, Aug., 1940.

## Occult Blood\*

With a Note on the Use of Carmine for the Marking of Stools

By

M. KIRSCHEN, M.D., H. SORTER, M.D.

and

H. NECHELES, M.D., Ph.D.

CHICAGO, ILLINOIS

A POSITIVE test for blood in the stool may be of grave importance to the clinician and to the patient. Yet a study of the literature and our own experience have impressed us with the fact that methods and evaluation of tests are not definitely settled. It seems to be accepted by most physicians, that a repeatedly negative benzidine test proves definitely the absence of a bleeding lesion in the alimentary canal. Boas (1, 2), who has introduced the concept of occult hemorrhage, has made the statement that only a positive test is of diagnostic importance and that a negative one does not exclude the possibility of occult bleeding and therefore should not always be relied upon. Abrahams (3) found that ingestion of 1 cc. of human blood was necessary to produce a positive benzidine test in the stool. No mention was made about details of the methods. Bramkamp (4) compared the results of the benzidine ether extract test when the same amounts of blood were mixed with equal weights of feces or water. He found the sensitivity of the test reduced one-fifth in case of feces. Three and one-half grams of fresh blood given by mouth gave a positive ether extraction and slide test in the feces, while 3.0 grams did not. Two grams of dried blood in a gelatine capsule gave a positive test. Ninety times as much blood was needed to give a positive reaction

when taken by mouth as was necessary when the blood was mixed with the feces. Digestion of blood with gastric juice and incubation of blood with feces did not reduce the peroxidase effects of the blood materially, but digestion with pancreatic enzymes did. Kiefer (5) found that a daily ingestion of at least 5 cc. of blood was necessary to give a positive benzidine test in the stool.

The most commonly used method for detection of blood in stool is essentially the slide benzidine test of Gregersen (6) (v.i.). Kiefer (5) has reiterated that the benzidine test is more sensitive, when performed with ether extract of the feces, and has added that the extract-tolidin test was even more accurate. Nevertheless, for routine clinical tests, Kiefer recommends the direct application of the reagents to the feces (i.e. Gregersen's test) (5, p. 532.) The reason for the wide use of the benzidine slide test seems to be its simplicity, and furthermore that the ether extract tests are considered as too sensitive, yielding positive results in a number of clinically normal persons on a meat free diet (6, 7), amounting, in the experience of one of us (M. K.), to as much as one-third of a normal, unselected group of subjects. It is evident that a certain amount of blood on its way through the alimentary tract is broken down into compounds which no longer yield a peroxidase reaction, or that substances in the feces may be able to inhibit this reaction (4), so that whatever peroxidase

\*From the Department of Gastro-Intestinal Research of Michael Reese Hospital.  
Aided by the A. B. Kuppenheimer Fund.  
Submitted April 15, 1941.

test is used, more or less small hemorrhages may remain undetected. Kiefer (5) found that at least 2-4.5 cc. of blood had to be ingested to yield a positive tolidin test, and that even the spectroscopic hematorporphyrin test was not positive when less than 3 cc. of blood had been ingested (5, 7.) In addition to this it has been shown repeatedly, that minimal amounts of blood are found in the stools of a number of normal persons on a meat and vegetable free diet (6, 7.) Gregersen (6), therefore, devised his blood test for feces with the idea in mind to make it only sensitive enough to detect quantities of fecal blood above those found in a number of normals, as explained above.

The main problem in our work was, therefore, not the elaboration of a more delicate test, but the evaluation of how much blood may become peroxidase negative after its way through the alimentary canal, and a method to diminish such destruction. One of us (M. K.) in collaboration with the late Boas,\* began work on this subject in 1937, which was discontinued in 1938. The interest in this problem had been aroused in another one of us (H. N.) by his observation during gastroscopy, of a freely bleeding gastric ulcer in a patient in whom repeated stool examinations before and after gastroscopy did not reveal blood (benzidine slide test.)

### METHODS

Sixty-six subjects were kept on a meat free diet until the end of the experiment. Only persons without pathology of the gastro-intestinal tract were used. The subjects were members of the laboratory, patients in the hospital and, most of them, from a Home for the Aged.† They were of both sexes, with an average age of 55 years. When a negative stool test had been obtained 1.5 or 2 grams of ox hemoglobin was administered orally in five equally divided doses in gelatin capsules during one day. Administration in divided doses rather than a single dose, was decided upon, in order to simulate hemorrhage more closely.

The stools were examined for occult blood, 24, 48, 72 and 120 hours after intake of the first dose of hemoglobin. The Gregersen benzidine test was performed in the following way: A piece of feces was taken from the inside of a scybalum; the piece was smeared over a glass slide and a small quantity of freshly prepared benzidine glacial acetic acid solution was rubbed into the spread film. A few drops of a 3 per cent hydrogen peroxide solution were added and the presence or absence of a blue color noted. The results were valued according to the intensity of the blue color as 1 to 3 plus. The guaiac, ether extract, and tolidin tests were employed as controls on a number of specimens.

### RESULTS

Using the benzidine slide test, 24 of the 66 subjects yielded a positive reaction for occult blood approximately 12 hours after administration of the last dose of hemoglobin. Of these, 10 were one plus, 13 were two plus and 1 was three plus. On the second day five, and on the third day three more subjects yielded positive reactions. In spite of the fact that a one plus reaction is usually discounted in routine examinations, we considered such cases as positives. Therefore, in an

unselected group of 66 normal persons the intake of 1.5 to 2 grams of hemoglobin was followed by a positive reaction for occult blood in the stools in only 32 subjects, i.e. in 48.5 per cent. The remaining 34 patients, i.e. 51.5 per cent, treated under the same conditions and in the same way as the others, were completely negative. Considerable individual variations were noted; with the same quantity of hemoglobin ingested, some subjects had 0, others 1 plus, others 2 plus and one three plus blood in the feces. Most positive reactions were found on the first, less on the second, and least on the third day following ingestion of hemoglobin.

The results obtained in Chicago are not in complete accord with those obtained previously with Boas, in which the percentage of negative cases was considerably higher; of 80 patients, 52 were negative, i.e. 65 per cent.‡ We believe that the difference in age between both groups of subjects accounts for the different results; the subjects studied in the first group were young individuals, while those examined here were mostly old people, with low gastric secretion. Ewald tests were performed on 16 of our subjects. Four had complete achlorhydria, 8 had no free acid and low combined acid, and the remainder had low free and combined acid. We believe that gastric HCl plays a significant rôle, possibly indirectly (4), in changes produced in hemoglobin passing through the gastro-intestinal tract.

Of a total number of 146 subjects in both series of tests, on a meat free diet until their stools were free of blood, and then fed with 1.5 to 2 grams of hemoglobin, only 60, i.e. 41 per cent gave a positive peroxidase reaction in the stools, while 86 subjects, or 59 per cent, were completely negative.

The guaiac and tolidin slide tests were performed on the stools of 12 subjects and found to yield nearly the same results as the routine benzidine test employed, while the ether extract test was positive in all of the 12 subjects.

Since our results left no doubt that relatively large quantities of blood are broken down in the alimentary canal to such a degree as to become peroxidase negative in the feces, a method was sought which would prohibit or decrease such destruction. Ten of our subjects on meat free diet, who had a negative benzidine stool reaction following ingestion of hemoglobin, were submitted to a second test. Two grams of hemoglobin were administered as before, but 10 ccs. of castor oil were given by mouth with the last dose of hemoglobin. All subjects experienced a slight diarrhea. Eight of them yielded benzidine positive stools, and only 2 remained negative.

The result demonstrated that a faster passage of hemoglobin through the intestinal tract apparently diminished the change of hemoglobin into compounds which cannot be identified by the peroxidase test. This assumption is supported by the findings of Ratnoff (8) and Snapper (7) that in normal small children the peroxidase test in the feces is positive with much smaller amounts of blood than in adults, which the latter considers to be related to the shorter length of, and the faster passage of material through the intestinal tract (7, p. 44.)

\*Died in Vienna on March 17, 1938, by suicide.

†We are greatly obliged to the Board, to Mr. M. Alexander, Director, and to the nurses of the Home for Aged Jews, Chicago, and to Drs. R. Green and H. Binzwanger, Attending Physicians to the Home

‡The same experimental procedure and technic was employed in both series.

In a number of experiments we have employed carmine to mark the feces when meat free diet was instituted. We have found that a number of preparations of carmine when given by mouth were able to produce positive peroxidase reaction in the stools. When these preparations were tested in vitro, some yielded positive peroxidase tests, while others did not; the latter must have undergone a change in the alimentary tract which made them acquire peroxidase characteristics. We have inserted the latter experience here, because carmine is used widely as marker for stools, and our experience may be of importance to other workers in this field. Recently it has been reported that carmine reduced gastric emptying time and lowered intestinal motility in children (11.) These latter results add to our objections against the use of carmine in certain experiments.

### DISCUSSION

Relatively large amounts of hemoglobin (corresponding to 9.4 and 12.5 ccs. of blood with 16 grams per cent of hemoglobin respectively), taken by mouth in small divided doses may, in a high percentage of persons, lose more or less their ability to give a positive peroxidase test after passing through the gastro-intestinal tract. One may assume therefore, that blood discharged in small amounts from lesions of the gastro-intestinal tract will undergo the same changes on its way throughout the stomach and intestines and therefore may not be detected in the feces by the routine benzidine method.

Why in some cases more, in others less, of hemin is destroyed in the gastro-intestinal tract; how much in normal individuals, and how much more in pathological conditions; why sometimes pure hemoglobin is excreted (the occult hemoglobin of Boas (9) and Schumm (10); what happens to hemoglobin in the absence of HCl in the stomach or in the alkaline environments of the small intestines, are all questions which have not yet been answered.

The discovery by Boas (1, 2) many years ago, that a positive test for occult blood in the feces is of greatest diagnostic value has been tested and verified by a large clinical experience. We know that the presence of occult blood is indicative of ulcer and carcinoma, and lately we have again been shown that inflammation of the gastric mucosa is able not only to give a positive benzidine test for occult blood, but to produce massive hemorrhage, also. This has been proven in many cases by gastroscopic examination in which the gastric mucosa was found to be either bleeding diffusely, or to be friable and bleeding readily.

The usual characteristic feature of hemorrhage from gastritis is the alternating appearance and disappearance of occult blood in the stools in spite of treatment and amelioration of symptoms; in ulcers the hemorrhage stops with rest and diet, whereas in carcinoma the positive reaction is continuously present for a long period of time.

Nevertheless it has to be borne in mind that negative stool tests or the disappearance of a positive benzidine reaction in the stool does not necessarily mean the absence or the disappearance of pathologic processes. Much more blood than hitherto believed is

needed to produce occult blood in the feces in many individuals by factors which are not yet well understood. They seem to have the ability to destroy more hemoglobin than others, changing the blood into bodies which cannot be demonstrated by the ordinary routine benzidine test.

It is evident that all tests for blood in the stools have a relative value only, insofar as none of them can detect amounts of blood below certain limits. In other words, small amounts of blood cannot be detected by any of the existing tests, even not by the spectroscopic hematoporphyrin test (5, 7.) What seems to us most important is that different individuals are able to destroy varying amounts of hemoglobin in their alimentary tract and that whatever method for the detection of occult bleeding is used, the clinician must be aware of the relative value of all methods and must not rely entirely on negative stool tests when, for example, a small, bleeding carcinoma of the gastro-intestinal tract is suspected, but must use his clinical judgement and all other available laboratory methods like X-ray gastroscopy, etc., as well.

We suggest, therefore, in suspicious cases with a negative peroxidase test, to pay more attention to other clinical or laboratory findings, to use the feeding of 1.5 grams of hemoglobin as a new test, in order to see whether the individual in question does not destroy unusually large amounts of hemoglobin in his intestinal tract, or to administer 10 cc. of castor oil after 3 meat free days and to repeat the peroxidase test.

### SUMMARY

One hundred and forty-six normal persons without gastro-intestinal complaints were kept on meat free diets until their stools were negative to the routine benzidine slide test. Then 1.5 to 2 grams of hemoglobin (corresponding to 9.4 or 12.5 ccs. of blood with 16 grams per cent hemoglobin content) was administered orally in 5 doses, evenly distributed over one day. All stools were examined during the 5 following days. Forty-one per cent of the 146 subjects had occult blood in their feces, while fifty-nine per cent had none. The significance of these experiments is discussed, and two new tests for the detection of occult bleeding in the gastro-intestinal tract are proposed. Carmine per se, when used for marking of stools, may yield a positive test for blood in the feces.

### REFERENCES

1. Boas, I.: Ueber Okkulte Magenblutungen. *Dtsch. Med. Wochenschr.* 20:1801.
2. Boas, I.: Die Lehre von den okkulten Blutungen. Leipzig, G. Thieme, 1914.
3. Abrahams, A.: The Test for Occult Blood in the Stools. *Lancet*, 199:420, Aug., 1920.
4. Bramkamp, R. F.: The Benzidine Reaction. *J. Lab. and Clin. Med.*, 14:1087, July, 1929.
5. Kiefer, E. D.: Detection of Occult Blood in Feces. *Am. J. Surg.* 25:530, Sept., 1934.
6. Gregersen, J. P.: Untersuchungen Ueber Okkulte Blutungen. *Arch. Verd. Kerkh.*, 23:54 and 133, 1919 and 25:169, 1919.
7. Snapper, I. and van Creveld, S.: Ueber Okkulte Magenblutungen. *Ergebn. d. Inn. Med. u. Kinderheilk.*, 32:1, 1927.
8. Ratnoff, H. L.: Ueber das Vorkommen von Okkultem Blut in den Stühlen im Frühen Kindesalter. *Zeitschr. f. Kinderheilk.*
9. Boas, I.: Die Bedeutung des Hämoglobins für die Diagnose des Magen- und Darmkanals. *Klin. Wochenschr.*
10. Schumm, O.: Die Spektrochemische Analyse natürlich vorkommender Farbstoffe. Fischer, Jena, 1927.
11. Macy, I. G., Reynolds, L. and Sonders, H. J.: The Effects of Carmine Upon the Gastro-Intestinal Motility of Children. *Am. J. Physiol.*, 125:75, May, 1939.

## Studies on Old Age

### V. Active Pancreatic Secretion in the Aged\*

By

H. NECHELES, M.D., Ph.D., F. PLOTKE, M.D.

and

JACOB MEYER, M.D.

CHICAGO, ILLINOIS

IN previous reports we have been able to show that resting and stimulated secretion of saliva is significantly lower in volume and amylase content in old people (1.) This observation led us to further investigate the digestion of the aged. In our next communications we reported that the concentration of pepsin and hydrochloric acid in the fasting gastric juice, and of amylase, trypsin and lipase in the fasting duodenal juice showed a significant depression in the aged (2, 3.) In another paper the clinical significance of these findings was discussed (4.) In the present paper we wish to report the results of studies on the duodenal juice in old people following stimulation of the pancreas.

**Procedure:** The old group consisted of male inmates of a home for the aged near Chicago,† varying in age between 43 and 87 years, with an average of 66.5 years. A control group of young people consisted of 30 persons between the ages of 18 and 35, with an average of 23.4 years. They were male students, research workers and technicians in the laboratory. The subjects in both groups were healthy except for some disabilities of old age in the older group.

The experimental procedure was as follows: Nothing was taken by mouth after 8 o'clock the night preceding the test. At 8 o'clock of the morning of the experiment a double barrelled tube was passed through the mouth into the duodenum. One lumen of the tube opened into the stomach for the constant removal of the gastric contents and the other lumen opened into the duodenum at about the height of the pancreatic duct. This procedure eliminated or decreased the dilution and impairment of pancreatic enzymes by gastric juice. The location of the tip of the duodenal tube was not ascertained by fluoroscopy but the constant appearance of clear gastric juice from one lumen of the double tube, and alkaline and usually bile stained duodenal juice from the other lumen made us feel certain about the correct location of the duodenal tip of the tube. Utilizing the procedure of McClure (5), a mixture of 5 cc. of oleic acid and 45 cc. of warm tap water was injected slowly into the duodenum. The proximal end of the duodenal tube was then closed for 15 minutes. At the end of that period duodenal contents were withdrawn. The first sample usually contained some oleic acid and was discarded. After that, duodenal juice was collected for 30 minutes. Samples

containing gall bladder bile were not used for analysis. All samples of the 30 minute period were pooled and used for chemical determinations. The bicarbonate content was determined by titration against 0.1 N HCl, and the value expressed in cubic centimeters of 0.1 N HCl. Amylase was determined by the method of Ross and Shaw (6) and the results expressed as maltose units. Lipase was determined by the method of Cherry and Crandall (7) and the results expressed in ccs. N 20 HCl. Trypsin was determined by the Anson and Mirsky (8) method and the values expressed in milligrams of tyrosin.

#### RESULTS

Table I presents all the data obtained. It is given completely, because these data will be of importance in later analysis of normal pancreatic secretion. Table II presents the statistical analysis and summary of the results.‡

The volume of duodenal juice obtained within the 30 minute period after the injection of oleic acid into the duodenum was nearly identical for the younger and older group. We cannot expect, of course, to obtain the entire volume of pancreatic secretion by the procedure employed. The rapid movement of fluid through the duodenum in normal persons makes it probable that only part of the pancreatic secretion can be obtained under any circumstances. The agreement between the volumes in the old and younger group therefore may be due to strict adherence to standard procedure in every experiment, but it may be that a much larger group of experimental subjects would show a difference. The above objections do not apply to the following determinations. Bicarbonate concentration in the duodenal juice was significantly higher in the group of old persons, the difference being +13%. Recent research (5) has shown that the secretion mechanism is mainly responsible for the secretion of bicarbonate by the pancreas, and secretin is liberated from the mucosa of the upper small intestine following the entrance into it of acid gastric juice. Others (9) and we have shown that the average acidity of gastric juice in the aged is relatively low. On the other hand it is known (see 5) that under pathological conditions a dissociation between various components of pancreatic secretion may occur and we can assume therefore for the time being that the increase of bicarbonate in the duodenal juice of old people may be due to certain changes occurring in the pancreas of old people, which will affect one fraction

\*Aided by the John Gottlieb Fund.

†We are obliged to Drs. Eugene Chesrow and James Walsh, and to the Administration of the Oak Forest Infirmary for their permission to work in the Infirmary and for their kind help.

‡From the Department of Gastro-Intestinal Research, Michael Reese Hospital.

Submitted August 15, 1941.

‡We are obliged to Mr. James Oliver for the statistical analysis.

of the pancreatic secretion more than the other fractions.

Amylase concentration was higher in the case of the older group than of the younger one, the difference being  $\pm 11\%$ . The difference is significant statistically, but biologically it may not be of great importance. In view of our previous findings of a decreased amylase content in the saliva of old people, this finding may be important, however. Our results do not enable us to say whether the increase of pancreatic amylase will make up for the relatively greater decrease in salivary amylase in old people. This point must be proven in further experiments on digestion and tolerance of carbohydrates in old people.

The lipase in the duodenal juice of the old group was significantly lower, the difference being  $-21\%$ . This lower lipase secretion is believed to be of biological importance in the digestion of fats since the pancreas is the main source of lipase in the intestines.

Trypsin in the duodenal juice was slightly lower in the older group, but this difference was not found to be statistically significant. The latter finding is of

importance in view of the lowered pepsin secretion in old people. This deficiency may be made up in part by the normal secretion of trypsin by the pancreas. Trypsin is not secreted by the intestinal mucosa. We have to bear in mind of course, that the first step in the digestion of proteins is in the stomach, and that pepsin is deficient in the average aged person.

### COMMENTS

In comparing the above results on stimulated pancreatic secretion with those obtained previously on the basal secretion of duodenal juice (2), the following can be said: In old people the concentration of pancreatic amylase in fasting duodenal juice was slightly lower than in a younger control group, while following stimulation of pancreatic secretion it was found increased. This difference between the two groups may be explained either by less intermittent fasting pancreatic secretion in the older group, or by a smaller secretion of intestinal amylase in old people.

In our previous work the lipase content of the fasting duodenal juice was found to be significantly lower in the older group of subjects. The same result was

TABLE I  
*Stimulated pancreatic secretion in a group of young and in a group of aged normal male subjects*

| No. | Patient | Years of Age | Volume cc. | Per Cent NaHCO <sub>3</sub> Content | Units of |        |          | No. | Patient | Years of Age | Volume cc. | Per Cent NaHCO <sub>3</sub> Content | Units of |        |         |
|-----|---------|--------------|------------|-------------------------------------|----------|--------|----------|-----|---------|--------------|------------|-------------------------------------|----------|--------|---------|
|     |         |              |            |                                     | Amylase  | Lipase | Trypsin  |     |         |              |            |                                     | Amylase  | Lipase | Trypsin |
| 1   | B. O.   | 25           | 22         | 0.17                                | 21.20    | 6.35   | 0.00954  | 1   | E. P.   | 72           | 88         | 0.19                                | 24.54    | 5.74   | 0.00102 |
| 2   | W. S.   | 20           | 43         | 0.15                                | 24.56    | 5.52   | 0.00638  | 2   | M. N.   | 55           | 33         | 0.60                                | 19.48    | 7.55   | 0.00701 |
| 3   | M. W.   | 21           | 33         | 0.09                                | 23.00    | 8.45   | 0.00765  | 3   | C. O.   | 59           | 33         | 0.19                                | 24.52    | 4.75   | 0.00141 |
| 4   | D. W.   | 32           | 37         | 0.14                                | 23.23    | 7.22   | 0.00294  | 4   | H. K.   | 64           | 35         | 0.16                                | 19.21    | 6.70   | 0.00105 |
| 5   | B. M.   | 24           | 57         | 0.17                                | 16.00    | 9.75   | 0.00812  | 5   | P. C.   | 73           | 26         | 0.13                                | 22.88    | 7.60   | 0.00774 |
| 6   | E. S.   | 19           | 62         | 0.19                                | 22.24    | 9.55   | 0.00264  | 6   | M. G.   | 76           | 30         | 0.16                                | 23.92    | 7.50   | 0.00704 |
| 7   | S. M.   | 18           | 28         | 0.13                                | 22.64    | 7.65   | 0.00110  | 7   | W. E.   | 70           | 21         | 0.14                                | 24.32    | 3.40   | 0.0123  |
| 8   | D. K.   | 35           | 22         | 0.15                                | 18.23    | 6.60   | 0.00355  | 8   | A. G.   | 57           | 69         | 0.16                                | 20.03    | 6.60   | 0.00134 |
| 9   | J. F.   | 23           | 21         | 0.11                                | 19.16    | 7.90   | 0.00766  | 9   | A. O.   | 59           | 42         | 0.14                                | 20.04    | 7.30   | 0.00122 |
| 10  | K. K.   | 24           | 26         | 0.09                                | 19.80    | 7.10   | 0.00625  | 10  | J. C.   | 43           | 55         | 0.17                                | 16.48    | 6.42   | 0.00915 |
| 11  | F. S.   | 29           | 58         | 0.13                                | 12.24    | 7.55   | 0.00432  | 11  | J. K.   | 52           | 71         | 0.03                                | 22.92    | 6.92   | 0.00820 |
| 12  | W. R.   | 20           | 18         | 0.14                                | 21.04    | 7.15   | 0.00576  | 12  | T. S.   | 78           | 47         | 0.17                                | 21.50    | 6.83   | 0.01531 |
| 13  | B. B.   | 24           | 27         | 0.17                                | 20.68    | 6.85   | 0.00728  | 13  | A. S.   | 64           | 65         | 0.17                                | 22.82    | 5.85   | 0.00144 |
| 14  | C. D.   | 21           | 25         | 0.17                                | 21.20    | 9.15   | 0.00123  | 14  | H. T.   | 51           | 65         | 0.18                                | 22.16    | 5.31   | 0.00149 |
| 15  | R. R.   | 19           | 63         | 0.12                                | 15.60    | 9.60   | 0.00109  | 15  | K. D.   | 57           | 24         | 0.10                                | 23.60    | 7.95   | 0.00338 |
| 16  | C. W.   | 22           | 42         | 0.10                                | 15.56    | 9.00   | 0.00699  | 16  | J. S.   | 48           | 46         | 0.17                                | 22.52    | 4.05   | 0.00355 |
| 17  | D. K.   | 27           | 34         | 0.18                                | 23.16    | 5.05   | 0.00359  | 17  | W. R.   | 71           | 45         | 0.15                                | 21.92    | 7.25   | 0.00552 |
| 18  | J. P.   | 22           | 28         | 0.16                                | 20.44    | 7.25   | 0.00129  | 18  | P. J.   | 66           | 54         | 0.19                                | 23.76    | 6.55   | 0.00358 |
| 19  | J. A.   | 22           | 42         | 0.14                                | 20.84    | 7.50   | 0.0020   | 19  | W. H.   | 82           | 35         | 0.15                                | 26.84    | 5.35   | 0.00105 |
| 20  | A. B.   | 23           | 68         | 0.11                                | 22.20    | 6.40   | 0.00599  | 20  | J. S.   | 71           | 52         | 0.11                                | 22.76    | 4.80   | 0.00177 |
| 21  | K. H.   | 27           | 64         | 0.16                                | 20.40    | 7.35   | 0.00344  | 21  | J. F.   | 74           | 21         | 0.12                                | 22.50    | 5.60   | 0.00127 |
| 22  | C. R.   | 24           | 75         | 0.15                                | 20.84    | 8.20   | 0.00279  | 22  | F. H.   | 63           | 59         | 0.15                                | 20.25    | 6.42   | 0.00195 |
| 23  | F. R.   | 24           | 28         | 0.12                                | 17.04    | 6.15   | 0.00285  | 23  | E. S.   | 69           | 43         | 0.16                                | 22.84    | 5.15   | 0.00371 |
| 24  | F. L.   | 24           | 55         | 0.18                                | 17.08    | 6.50   | 0.00405  | 24  | R. S.   | 68           | 72         | 0.13                                | 18.68    | 6.90   | 0.00453 |
| 25  | L. A.   | 24           | 42         | 0.13                                | 20.48    | 7.05   | 0.00127  | 25  | F. J.   | 75           | 27         | 0.17                                | 21.57    | 3.85   | 0.00254 |
| 26  | W. S.   | 21           | 62         | 0.09                                | 17.00    | 7.25   | 0.00664  | 26  | M. H.   | 64           | 16         | 0.14                                | 17.68    | 5.70   | 0.00500 |
| 27  | G. H.   | 24           | 49         | 0.13                                | 19.24    | 8.70   | 0.000323 | 27  | J. M.   | 63           | 29         | 0.16                                | 21.52    | 4.95   | 0.00353 |
| 28  | M. F.   | 21           | 63         | 0.11                                | 18.20    | 8.35   | 0.00996  | 28  | P. B.   | 80           | 32         | 0.14                                | 20.60    | 6.60   | 0.00177 |
| 29  | P. B.   | 23           | 68         | 0.18                                | 16.72    | 8.05   | 0.00115  | 29  | V. E.   | 87           | 28         | 0.13                                | 21.48    | 6.85   | 0.00177 |
| 30  | H. B.   | 21           | 22         | 0.14                                | 20.32    | 8.85   | 0.00492  | 30  | J. C.   | 73           | 56         | 0.17                                | 24.12    | 5.75   | 0.00144 |

obtained now with stimulated pancreatic secretion. The relatively great difference of  $-21\%$  is believed to be due to a deficiency of pancreatic secretion which is the main source of the lipase found in the small intestine, although we do not know whether oleic acid stimulates intestinal secretion of lipase.

Trypsin had been found to be significantly lower in the fasting duodenal juice of older people (2.) In the present work on stimulated pancreatic secretion no

vary secretion in old people and the dryness of the mouth resulting therefrom, may, however, induce these persons to drink more fluids with their meals. We have no observations on this question, but if this is true, a factor of dilution will have to be considered besides. Examination of the feces of old people on diets containing varying amounts of starch may further elucidate this question.

The significant lowering of lipase secretion by the

TABLE II  
Summary and analysis of results

|                    |       | Range           | Mean    | Standard Deviation | Standard Error       |
|--------------------|-------|-----------------|---------|--------------------|----------------------|
| Volume             | Young | 18-75           | 43.07   | 17.223             | 9.887                |
|                    | Old   | 16-88           | 44.43   | 16.113             | 9.617                |
| NaHCO <sub>3</sub> | Young | 0.09-0.19       | 0.14    | 0.9129             | 0.000278             |
|                    | Old   | 0.09-0.19       | 0.1583* | 0.08583            | 0.0002456            |
| Amylase            | Young | 15.56-24.56     | 19.921  | 2.395              | 0.191                |
|                    | Old   | 16.48-26.84     | 21.937* | 1.984              | 0.131                |
| Lipase             | Young | 5.05-9.75       | 7.601*  | 1.155              | 0.044                |
|                    | Old   | 3.4-7.95        | 6.02    | 1.162              | 0.045                |
| Trypsin            | Young | 0.00032-0.0096  | 0.0048  | 0.0028             | 255 $\times 10^{-9}$ |
|                    | Old   | 0.00106-0.01500 | 0.0044  | 0.0036             | 413 $\times 10^{-9}$ |

\*Denotes that the difference between the values of both groups is statistically significant.

such difference was found. Since trypsin is secreted by the pancreas only and not by the intestinal mucosa, the above difference may be due to less intermittent fasting pancreatic secretion in old people.

The completion of the work reported above enables us to make certain tentative statements about digestion and nutrition in the aged. Concerning the digestion of starch in old people, the diminished volume and amylase content of stimulated salivary secretion certainly will impair the first phase of starch digestion following its ingestion.

The slightly increased contents of amylase in the duodenal juice following stimulation of the pancreas will make up somewhat for the deficiency of the amylase in the saliva. The low volume of stimulated sali-

pancreas suggests that the fat content in the diet of old persons should not be too high.

### SUMMARY

The pancreatic secretion of a group of 30 aged subjects with an average age of 66.5 years was compared with that of a group of 30 young persons with an average age of 23.4 years. Pancreatic secretion was stimulated by the intraduodenal injection of oleic acid. The following results were obtained: Bicarbonate and amylase content was significantly increased in the older group. Lipase was  $21\%$  lower in the aged subjects. Volume of fluid and trypsin concentration were not significantly different in both groups. These results and their application to digestion and nutrition in old people have been discussed.

### REFERENCES

1. Meyer, J., Golden, J. S., Steiner, N. and Necheles, H.: The Ptyalin Content of Human Saliva in Old Age. *Am. J. Physiol.*, 119:600, July, 1937.
2. Meyer, J., Spier, E. and Neuwelt, F.: Basal Secretion of Digestive Enzymes in Old Age. *Arch. Int. Med.*, 65:171, Jan., 1940.
3. Meyer, J. and Necheles, H.: Studies in Old Age. IV. The Clinical Significance of Salivary, Gastric and Pancreatic Secretion in the Aged. *J. A. M. A.*, 115:2050, Dec. 14, 1940.
4. Meyer, J.: The Management of Diseases of the Gastro-Intestinal Tract in the Aged. Clinic of Dr. Jacob Meyer. *Med. Clinics of North America*, 24:3, Jan., 1940.
5. McClure, C. W.: Functional Activities of the Pancreas and the Liver. Medical Author's Publishing Co., New York, 1937.
6. Ross, J. R. and Shaw, M. M.: Determination of Pancreatic Amylase. *J. Biol. Chem.*, 104:131, 1934.
7. Cherry, J. S. and Crandall, L. A.: The Specificity of Pancreatic Lipase. *Am. J. Physiol.*, 100:266, 1932.
8. Anson, M. L. and Mirsky, A. E.: Determination of Proteases. *J. Gen. Physiol.*, 16:59, 1932; 17:151, 1933.
9. Osterberg, A. L., Vanzant, F. R., Alvarez, W. C. and Rivers, A. B.: Studies of Pepsin in Human Gastric Juice. *Am. J. Dig. Dis. and Nutrit.*, 3:35, 1936.



## Studies on Old Age

### VI. Blood Enzymes in the Aged\*†

By

JACOB MEYER, M.D., H. SORTER, M.D.

and

H. NECHELES, M.D., Ph.D.

CHICAGO, ILLINOIS

IN a series of previous publications we have been able to show changes in the digestive ferments of old people. The volume and amylase content of salivary secretion was found to be significantly diminished in the aged (1, 2.) Pepsin and hydrochloric acid of the gastric juice has been reported by others and ourselves to be lower in old people (2, 5.) In a recent study we found that the lipase contents of the stimulated pancreatic secretion in old persons was significantly lower than that in a comparable control group of young persons, the difference being -21% (6.)

Dehydration and a change in the fat tissues of the body are recognized phenomena in aged persons. An atrophy of the fatty tissues as well as a change in composition and color of the fat occurs (7.) The cause of this change in the fatty tissues in the aged is not known (8.) Old people are reported to have a tendency for lipemia (9.) Sakai (10) stated that this tendency may be related to a diminution of blood lipase in old persons. Serum lipase has been found diminished in many cases of cachexia, indicating perhaps a diminution of cellular activity in general (11.) Nitzulescu, Ornstein and Herescu have found decreased serum esterase (tributyryl) in old people (12.) The findings quoted above, together with our own observations of a lowered pancreatic secretion of lipase in the aged led us to investigate the concentration of the lipase in the serum of old persons. We were aware of the fact that neither the origin nor the function of the blood lipase are definitely known, but this will be discussed below.

#### PROCEDURE

The "old group" consisted of 26 subjects of males and females from a home for the aged, varying in age between 61 and 89, with an average age of 77 years. The "young" control group consisted of internes, technicians and workers in this hospital, both males and females, varying in age between 19 and 39, with an average of 27 years. All subjects were normal except for the debilities of old age in a number of members of the first group. For 12 hours previous to the test nothing was taken by mouth. Then venous blood was withdrawn with slight constriction of the fore-arm into a dry syringe. The blood was emptied into a dry test tube and left to clot. The supernatant serum was employed for determination of lipase by a modification of the Crandall and Cherry method (13), and of diastase

by the Ross and Shaw method (14.) The lipase level of the serum is expressed in N/20 ecs. of NaOH; and the diastase concentration in Somogyi units. Blood pressure, hemoglobin and red blood count was taken. Serum protein was determined by the modified Barbour and Hamilton method (15) and expressed as gram per cent.

#### RESULTS

Serum diastase was 113 Somogyi units in the older group and 114 Somogyi units in the younger group.

The serum lipase was 1.50 units in the older group and 2.04 units in the younger group, i.e. 26.5% lower in the older group. If serum diastase and lipase concentration of the older group are recalculated on the basis of the serum protein concentration of the younger group, i.e. 6.98 gm. % instead of 7.38 gm. % of the older group, the values would be 107 units for the diastase and 1.42 units for the lipase. That would mean no appreciable difference in the diastase of the old and younger group (-6%), but a significant difference of -30.4% for the lipase of the older group.

The average blood pressure in the group of old subjects was 136/72 as compared to 118/70 in the younger group.

Hemoglobin in the older group was 75% Sahli, while in the younger group it was 81%. This finding is well known to clinicians. The lower hemoglobin in the aged may in part be due to lowered acid secretion of the stomach and the consequently diminished utilization of iron from the diet. The red blood count in the older group was 3.85 millions as compared to 4.14 millions in the younger group. This latter finding parallels the hemoglobin values.

The serum protein content in the older group was 7.38, while in the younger group 6.98 gram % were found. This higher protein concentration in the serum of old people can be explained by the dehydration of old persons (7.)

#### DISCUSSION AND COMMENTS

Our findings on the difference of blood pressure, hemoglobin and red blood count of old and young persons confirm what is already known. The increased serum protein content in the blood of old persons may be correlated with the well known fact of dehydration in old people. The difference between serum lipase concentration in the blood of young and old persons is considerable and significant. It is of interest to note that the values for serum diastase and lipase parallel those found in the duodenal juice following stimulation of the pancreas which we reported in a previous

\*Aided by the John Gottlieb Fund.

†We are greatly obliged to the Board, to the Director, Mr. M. Alexander, and to the Nursing Staff of the Home for Aged Jews, Chicago, and to Drs. R. Green and H. Binswanger, Attending Physicians to the Home.

From the Department of Gastro-Intestinal Research, Michael Reese Hospital.  
Submitted August 15, 1941.

communication (6): namely, no significant difference between the old and young group in diastase and a markedly lowered lipase in the older group, the difference amounting to —21%. This correlation is naturally of interest in relation to the aging process, but it is of interest as well in relation to the various

theories about the origin of blood enzymes. As stated above we do not know whether blood enzymes are waste products of cellular metabolism in general as assumed by Carlson and Luckhardt (16) and others, or whether they are derived from the pancreas, from the liver or other organs. For a discussion of this

*Blood enzymes in old and young persons*

| Old Group                        | Age in Years | Weight in Kg. | Blood Pressure Systolic/Diastolic | Hemoglobin Per Cent Sahli | Red Cell Count in Millions | Serum Protein Gram Per Cent | Serum Diastase Units | Serum Lipase ccm. N/20 NaOH |
|----------------------------------|--------------|---------------|-----------------------------------|---------------------------|----------------------------|-----------------------------|----------------------|-----------------------------|
| <b>Females</b>                   |              |               |                                   |                           |                            |                             |                      |                             |
| 1                                | 86           | 47.25         | 128/60                            | 74                        | 3.70                       | 6.89                        | 98                   | 2.14                        |
| 2                                | 82           | 71.10         | 168/50                            | 70                        | 3.67                       | 7.27                        | 174                  | 1.30                        |
| 3                                | 82           | 38.50         | 125/75                            | 70                        | 3.65                       | 7.35                        | 118                  | 1.22                        |
| 4                                | 80           | 68.85         | 128/68                            | 72                        | 3.80                       | 7.29                        | 120                  | 1.06                        |
| 5                                | 79           | 81.00         | 116/60                            | 77                        | 4.00                       | 7.24                        | 100                  | 1.54                        |
| 6                                | 79           | 53.30         | 134/76                            | 70                        | 3.68                       | 7.44                        | 100                  | 1.36                        |
| 7                                | 77           | 46.80         | 125/76                            | 76                        | 3.72                       | 7.15                        | 99                   | 1.20                        |
| 8                                | 75           | 54.00         | 146/76                            | 78                        | 3.95                       | 7.34                        | 105                  | 1.68                        |
| 9                                | 79           | 84.50         | 110/80                            | 74                        | 3.88                       | 7.28                        | 120                  | 1.60                        |
| 10                               | 74           | 57.60         | 130/78                            | 75                        | 3.80                       | 7.18                        | 100                  | 1.56                        |
| 11                               | 73           | 70.20         | 136/77                            | 76                        | 3.89                       | 7.55                        | 122                  | 2.04                        |
| 12                               | 72           | 51.70         | 124/72                            | 78                        | 3.90                       | 7.55                        | 100                  | 1.42                        |
| 13                               | 72           | 57.60         | 138/80                            | 58                        | 2.80                       | 7.99                        | 150                  | 1.90                        |
| 14                               | 68           | 55.50         | 128/65                            | 76                        | 3.80                       | 7.12                        | 118                  | 1.38                        |
| 15                               | 67           | 60.30         | 138/74                            | 78                        | 4.01                       | 7.38                        | 105                  | 1.58                        |
| 16                               | 61           | 69.80         | 132/68                            | 78                        | 3.75                       | 7.78                        | 100                  | 1.40                        |
| Average                          | 75           | 60.70         | 134/71                            | 74                        | 3.75                       | 7.36                        | 114                  | 1.52                        |
| <b>Males</b>                     |              |               |                                   |                           |                            |                             |                      |                             |
| 17                               | 89           | 57.15         | 120/80                            | 79                        | 4.00                       | 7.55                        | 108                  | 1.30                        |
| 18                               | 86           | 62.00         | 135/70                            | 74                        | 3.90                       | 7.99                        | 100                  | 1.40                        |
| 19                               | 84           | 57.70         | 148/76                            | 76                        | 3.99                       | 6.94                        | 100                  | 1.16                        |
| 20                               | 81           | 80.10         | 135/70                            | 82                        | 4.20                       | 7.32                        | 106                  | 1.50                        |
| 21                               | 81           | 65.25         | 128/80                            | 79                        | 4.00                       | 8.10                        | 125                  | 1.28                        |
| 22                               | 80           | 63.80         | 136/70                            | 78                        | 4.00                       | 6.98                        | 94                   | 1.84                        |
| 23                               | 79           | 85.00         | 145/70                            | 78                        | 4.20                       | 7.38                        | 112                  | 1.56                        |
| 24                               | 78           | 61.70         | 136/72                            | 78                        | 3.90                       | 7.22                        | 127                  | 1.58                        |
| 25                               | 73           | 47.70         | 153/70                            | 78                        | 4.00                       | 7.28                        | 120                  | 1.40                        |
| 26                               | 69           | 65.40         | 150/76                            | 75                        | 3.89                       | 7.32                        | 106                  | 1.36                        |
| Average                          | 80           | 64.88         | 139/73                            | 78                        | 4.01                       | 7.41                        | 110                  | 1.47                        |
| <b>Average Males and Females</b> | 77           | 62.32         | 136/72                            | 75                        | 3.85                       | 7.38                        | 113                  | 1.50                        |
| <b>Young Group Females</b>       |              |               |                                   |                           |                            |                             |                      |                             |
| 1                                | 39           | 58.50         | 128/70                            | 72                        | 3.80                       | 7.25                        | 115                  | 2.42                        |
| 2                                | 38           | 52.00         | 126/67                            | 70                        | 3.85                       | 7.13                        | 100                  | 2.04                        |
| 3                                | 37           | 54.75         | 120/70                            | 76                        | 4.00                       | 6.91                        | 98                   | 1.60                        |
| 4                                | 33           | 52.00         | 125/75                            | 79                        | 4.00                       | 6.68                        | 120                  | 1.98                        |
| 5                                | 32           | 50.00         | 129/70                            | 78                        | 3.95                       | 7.27                        | 100                  | 1.48                        |
| 6                                | 32           | 51.00         | 126/65                            | 90                        | 4.15                       | 6.82                        | 115                  | 1.80                        |
| 7                                | 29           | 52.00         | 127/76                            | 81                        | 4.15                       | 6.90                        | 116                  | 1.52                        |
| 8                                | 29           | 54.00         | 120/80                            | 79                        | 4.00                       | 7.06                        | 100                  | 1.80                        |
| 9                                | 28           | 58.50         | 118/76                            | 79                        | 4.00                       | 6.95                        | 95                   | 2.10                        |
| 10                               | 27           | 47.80         | 120/70                            | 77                        | 3.98                       | 6.71                        | 120                  | 1.90                        |
| 11                               | 25           | 62.00         | 125/75                            | 82                        | 4.15                       | 6.83                        | 120                  | 2.60                        |
| 12                               | 29           | 54.00         | 128/78                            | 75                        | 4.00                       | 7.41                        | 117                  | 2.14                        |
| 13                               | 22           | 51.00         | 115/70                            | 80                        | 4.15                       | 6.76                        | 120                  | 2.04                        |
| 14                               | 20           | 52.00         | 110/70                            | 80                        | 4.03                       | 6.78                        | 98                   | 1.80                        |
| 15                               | 20           | 67.50         | 115/76                            | 80                        | 4.10                       | 6.89                        | 125                  | 2.30                        |
| 16                               | 20           | 53.00         | 118/70                            | 78                        | 3.95                       | 6.97                        | 117                  | 3.50                        |
| 17                               | 20           | 60.00         | 110/65                            | 85                        | 4.30                       | 7.15                        | 119                  | 1.92                        |
| 18                               | 20           | 52.00         | 115/70                            | 83                        | 4.25                       | 6.82                        | 110                  | 2.04                        |
| 19                               | 19           | 52.00         | 110/70                            | 79                        | 4.05                       | 6.70                        | 138                  | 1.98                        |
| Average                          | 27           | 54.42         | 120/72                            | 79                        | 4.05                       | 6.95                        | 113                  | 2.05                        |
| <b>Males</b>                     |              |               |                                   |                           |                            |                             |                      |                             |
| 20                               | 33           | 56.00         | 118/70                            | 83                        | 4.28                       | 6.68                        | 100                  | 2.46                        |
| 21                               | 29           | 55.00         | 115/70                            | 88                        | 4.35                       | 7.29                        | 100                  | 2.00                        |
| 22                               | 27           | 64.00         | 110/65                            | 90                        | 4.52                       | 7.06                        | 125                  | 2.20                        |
| 23                               | 27           | 80.00         | 115/60                            | 88                        | 4.40                       | 7.05                        | 125                  | 2.00                        |
| 24                               | 27           | 72.00         | 110/70                            | 81                        | 4.38                       | 6.92                        | 118                  | 1.80                        |
| 25                               | 27           | 70.00         | 110/65                            | 81                        | 4.20                       | 6.36                        | 100                  | 1.84                        |
| 26                               | 27           | 71.00         | 118/67                            | 88                        | 4.50                       | 7.41                        | 174                  | 2.06                        |
| 27                               | 25           | 54.00         | 110/65                            | 80                        | 4.15                       | 6.89                        | 100                  | 1.80                        |
| 28                               | 22           | 54.00         | 110/60                            | 82                        | 4.20                       | 7.90                        | 110                  | 1.86                        |
| Average                          | 27           | 64.00         | 113/66                            | 85                        | 4.33                       | 7.06                        | 117                  | 2.00                        |
| <b>Average Males and Females</b> | 27           | 57.50         | 118/70                            | 81                        | 4.14                       | 6.98                        | 114                  | 2.04                        |

question, we refer the reader to articles by Davis and Ross (17), Somogyi (18) and to Oppenheimer's Handbook (19.)

### SUMMARY

In a group of old people varying in age between 61 and 89 with an average age of 77, and a control group of young people varying in age between 19 and 39, with an average of 27 years, blood studies were performed and the following average results obtained for the old and young group respectively:

1. Blood pressure 136/72 and 118/70.
2. Hemoglobin, 75 and 81% Sahli.
3. Red blood count, 3.85 millions and 4.14 millions.
4. Serum proteins, 7.38 and 6.98.

5. Serum diastase, 113 and 114 units.
6. Serum lipase, 1.50 and 2.04 units.
7. If the blood diastase and lipase values of the older group are recalculated on the basis of the serum protein concentration of the younger group, the values are 107 and 1.42 units respectively. The difference between the serum lipase in the young and in the aged, namely —30.4% is significant and considerable. Changes in fat metabolism in the aged may be responsible for this difference. The values for serum diastase and serum lipase parallel those found in previous work for the stimulated pancreatic secretion of diastase and lipase in young and old people. The significance of the findings is discussed.

### REFERENCES

1. Meyer, J., Golden, J. S., Steiner, N. and Neeches, H. P.: The Pepsin Content of Human Saliva in Old Age. *Am. J. Physiol.*, 119:600, July, 1937.
2. Meyer, J., Spier, E. and Neuwelt, F.: Basal Secretion of Digestive Enzymes in Old Age. *Arch. Int. Med.*, 65:171, Jan., 1940.
3. Meyer, J. and Neeches, H.: Studies in Old Age. IV. The Clinical Significance of Salivary, Gastric and Pancreatic Secretion in the Aged. *J. A. M. A.*, 116:2050, Dec. 14, 1940.
4. Meyer, J.: The Management of Diseases of the Gastro-Intestinal Tract in the Aged. *Clinic of Dr. Meyer. Med. Clinics of North America*, 24:9, Jan., 1940.
5. Osterberg, A. E., Vinnant, F. R., Alvarez, W. C. and Rivers, A. B.: Studies of Pepsin in Human Gastric Juice. *Am. J. Dig. Dis. and Nutrit.*, 3:35, March, 1936.
6. Neeches, H., Polke, F. and Meyer, J.: Studies in Old Age. V. Active Pancreatic Secretion in the Aged. *Am. J. Dig. Dis.*, 9:157, 1942.
7. McClay, C. M.: Chemical Aspects of Aging. Chapter 21 in Cowdry, E. V.: *Problems of Aging*, 1935, Williams and Wilkins Baltimore.
8. Wells, H. G.: Adipose Tissue, a Neglected Subject. Part I. *J. A. M. A.*, 114:2177, 1940.
9. Becquerel et Rodier; Parhon C., Parhon, M.; Timel; Parhon, C., Ornstein, I. and Sibi, M.: Quoted by 12.
10. Sakai: *Biochem. Zeitschr.*, 62:347, 1914. Quoted by 12.
11. Bauer: *Wien. klin. Wochenschr.*, 25:1376, 1912. Quoted by 12.
12. Nitulescu, Ornstein, I. and Herescu, D.: Recherches sur les Lipases Sériques. *Compt. Rend. des Séances et Mémoires de la Société de Biologie*, 114:747, 1933.
13. Kaplan, L., Cohn, D. J. and Reich, F.: Unpublished.
14. Ross, J. R. and Shaw, M. M.: Determination of Pancreatic Amylase. *J. Biol. Chem.*, 104:131, 1934.
15. Barbour, H. G. and Hamilton, W. F.: The Falling Drop Method for Determining Specific Gravity. *J. Biol. Chem.*, 69:525, 1926.
16. Carlson, A. J. and Luckhardt, A. R.: On the Diastases in the Blood and the Body Fluids. *Am. J. Physiol.*, 23:148, 1904.
17. Davis, L. H. and Ross, E. L.: The Source of Diastase in the Blood. *Am. J. Physiol.*, 66:22, 1921.
18. Somogyi, M.: Diastatic Activity of Human Blood. *Arch. Int. Med.*, 67:665, 1941.
19. Oppenheimer, C.: *Die Fermente und ihre Wirkungen*. Leipzig, 5th ed., Ernährungsband 1.

## The Effect of Magnesium Sulphate Upon the Sphincter of Oddi of Man

By

GEORGE S. BERGH, M.D.

and

JOHN A. LAYNE, M.D.

MINNEAPOLIS, MINNESOTA

THE use of magnesium sulphate as a drug to relax the sphincter of Oddi has been advocated for both diagnosis and therapy of biliary tract lesions. Therefore, we have undertaken to study the effect of this drug upon the sphincter by direct observations in patients with choledochostomy tubes.

### METHOD OF EXPERIMENTATION

Patients who previously had undergone cholecystectomy, choledochotomy and intubation of the common bile duct voluntarily submitted themselves as subjects for these studies. As a preliminary procedure, the anatomical status of the bile ducts was demonstrated to be normal by cholangiographic examination. Several weeks or months were allowed to intervene between the operation and the time of the experiments. The studies were carried out after the patients had fasted for eight hours.

The apparatus, which was sterilized in the autoclave, consisted of an infusion flask connected by a rubber tube to the choledochostomy tube. A Murphy drip bulb was included in the system so that observations of flow could be made. The fluid in the system

was sterile physiological salt solution. (See reference 1, Fig. 1.)

The sphincter resistance was measured by a method similar to that employed by Mann (2), Elman and McMaster (3) and others. By elevating or lowering the infusion flask, the pressure within the duet system could be altered, and it could be read directly on a centimeter scale which was set so that the zero point was at the estimated level of the common bile duct. The column of saline solution was adjusted to the level at which it was just supported without allowing any flow, and this pressure was recorded as *sphincter resistance*.

Measurements of sphincter resistance were made successively at intervals of one to several minutes. After fifteen to thirty minutes of preliminary measurements indicated that the resistance was stable, a dose of 12.5 grams of magnesium sulphate was administered (by mouth in one-half of the cases, and by duodenal tube in the remainder.) In all cases in which the tube was used, the position of its tip in the second portion of the duodenum was verified by roentgenoscopic examination. In seventeen cases the salt was dissolved in 30 cc. of water and administered either by mouth (9 cases) or by duodenal tube, (8 cases.) In

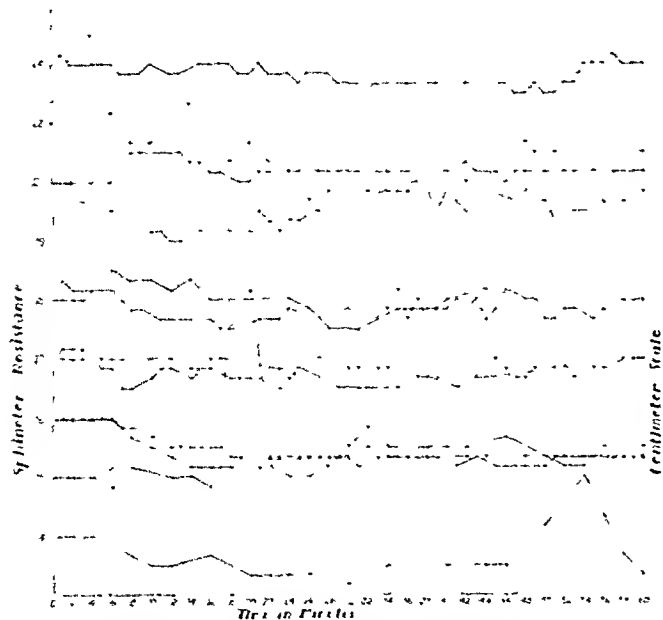


Fig. 1. Diagrams indicating the effect of the oral administration of magnesium sulphate upon the sphincter of Oddi in twelve human subjects. The sphincter resistance is recorded on the ordinate and the time in minutes after administration of the drug is recorded on the abscissa. The original stabilized sphincter resistance measured in terms of centimeters of saline solution pressure are indicated by the figures on the ordinate at the left, and the extent of variation may be measured according to the scale on the right, where each unit represents one centimeter.

25 cases it was dissolved in 50 cc. and administered by mouth (12 cases) and by duodenal tube (13 cases.) The duodenal instillation was done by gravity alone and usually required from three to five minutes. In all cases the solution was left in place and was not removed by aspiration. In 24 cases the measurements were made at frequent intervals throughout the experiment; in the remaining 18 instances no measurements were made during the twenty minutes immediately following the administration of the drug, but were resumed after that time.\*

Four groups of observations were made in these 42 experiments. In Group A the magnesium sulphate was given by mouth and measurements of sphincter resistance were continued during a period of one hour (excepted in one case in which measurements were discontinued after 44 minutes) after the administration of the salt. Group B included a similar series in which the drug was administered by duodenal tube. In Group C the salt was given by mouth, but a twenty minute interval was allowed to elapse between the time of administration of the magnesium sulphate and the resumption of measurements of sphincter resistance. This was done in order to avoid dilution and washing out of the solution by the perfusion fluid. Group D included a similar series in which the drug was administered by duodenal tube.

In order to determine the effective concentration of magnesium sulphate, five, ten, and twenty per cent solutions of the salt were introduced successively into the duodenum in doses of 30 cc. in each of three

\*The amount of saline which is introduced into the duodenum through the choledochostomy tube while measuring sphincter resistance during a twenty minute period may vary from 20 to 40 cc. The lapse of a twenty minute interval during which the tube is clamped and no measurements are made, therefore, avoids dilution and washing out of the magnesium sulphate solution.

patients (Group E.) Several hours were allowed to intervene between the introduction of each solution.

### OBSERVATIONS

In the series of 42 observations magnesium sulphate produced sphincter relaxation 33 times. The relaxation was preceded by an initial contraction in 17 of 24 cases (Groups A and B.) In most cases the decrease in sphincter resistance was small and of doubtful significance (one to four centimeters of saline solution pressure), but occasionally there was a striking fall (eight centimeters of saline solution pressure in one case.) In the 33 cases in which sphincter relaxation occurred, the average maximum fall was slightly less than 4 cm. of saline solution pressure. The maximum fall occurred within twenty-one to thirty minutes after

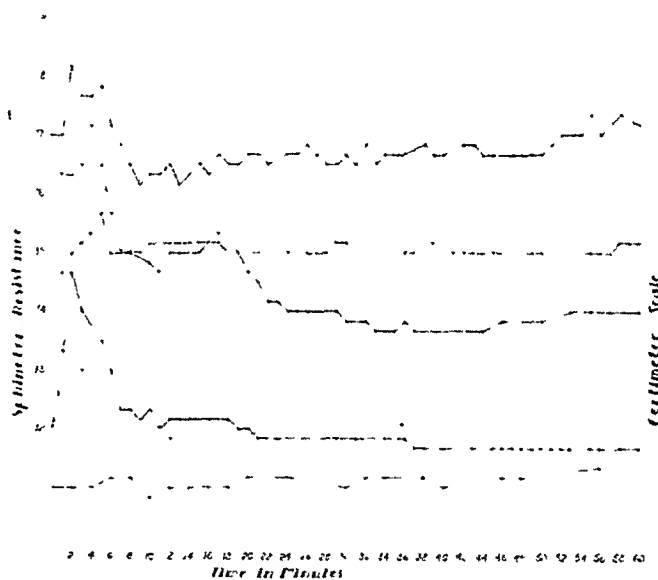


Fig. 2A

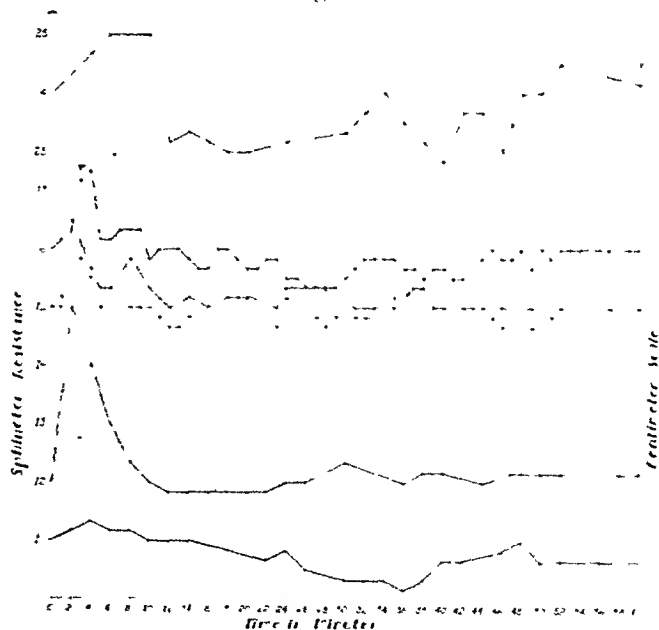


Fig. 2B

Fig. 2 (A and B.) Diagrams indicating the effect of the intraduodenal administration of magnesium sulphate upon the sphincter of Oddi in twelve human subjects. The method of recording is the same as in Fig. 1.

administration of the drug in most instances, but it occurred as early as twelve minutes in one patient, and as late as thirty-seven minutes in another.

**Group A.** In 12 patients the most frequent response was simple relaxation of the sphincter (6 cases.) In four cases there was an initial increase followed by a decrease in sphincter resistance. In one case there was an initial increase in resistance followed by a re-

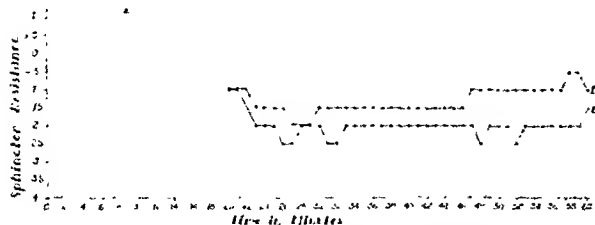


Fig. 3. Composite curve showing the effect of magnesium sulphate upon the resistance of the sphincter of the common bile duct. The original sphincter resistance level (zero level) represents the lowest readings obtained during the preliminary measurements which established the stability of the sphincter. Changes of the sphincter resistance from this level are recorded in centimeters of saline solution pressure on the ordinate. Time measurements, beginning immediately after administration of the drug, are recorded on the abscissa. A twenty minute interval occurred between the administration of the drug and the resumption of measurements of sphincter resistance. Graph C represents 9 cases in which magnesium sulphate was administered orally, and Graph D represents 9 cases in which the salt was instilled into the duodenum.

turn to the original tonus level, and in one case the drug caused a prolonged elevation of the sphincter resistance (Fig. 1.) In half of the cases the sphincter returned to the original tonus level within sixty minutes, but there was individual variation in this respect. The maximum relaxation of the sphincter occurred 12 to 30 minutes after the administration of the drug (average 21 minutes), and the average maximum fall was approximately 4 cm. of saline solution pressure.

**Group B.** In twelve patients who had been given magnesium sulphate by duodenal tube, the response of the sphincter (Figs. 2a and 2b) was similar to that demonstrated in Group A except that an initial contraction was prominent in this group. In seven instances there was an initial increase followed by a decrease in the sphincter resistance, in four cases there was an initial increase in resistance followed by a return to the original tonus level, and in one patient the drug had no effect. In no instance did simple relaxation of the sphincter occur without an initial contraction. In this group the average maximum decrease in sphincter resistance was approximately 3 cm. of saline solution pressure.

**Group C.** When a twenty minute interval was allowed to elapse between the time of the oral administration of magnesium sulphate and the resumption of measurements of sphincter resistance, obviously no information about the initial period of increased resistance could be obtained, since measurements were not made during the time it would be expected to occur. The maximum fall in sphincter resistance occurred twenty-six minutes after administration of the drug (Fig. 3.) The decreased tone persisted longer than in Group A, probably because of

the greater dilution and washing away of the relaxing agent by the perfusion fluid in Group A. In all nine patients of Group B, a decrease in sphincter resistance was observed, and this persisted for as long as seventy-five minutes in individual cases.

**Group D.** This group was similar to Group C in that the initial period of increased sphincter resistance was not demonstrated when a twenty minute interval was allowed to elapse between the time of intraduodenal administration of the magnesium sulphate and the resumption of measurements of resistance. The maximum fall in sphincter resistance was obtained in twenty-seven minutes (Fig. 3.) In the nine patients there was relaxation of the sphincter in seven, and no effect in two cases.

**Group E.** The effect in more dilute solutions of magnesium sulphate upon sphincter resistance is illustrated in Fig. 4, which represents the data obtained in one of the three cases. Five per cent solutions have little or no effect, whereas twenty per cent magnesium sulphate is as effective as a more concentrated solution.

### DISCUSSION

In 1917, Meltzer (4) suggested that if magnesium sulphate were introduced into the duodenum it might cause relaxation of the sphincter, and, probably also contraction of the gall bladder ("Law of Contrary Innervation.") Lyon (5) applied this suggestion to human patients and observed that the introduction of this drug into the duodenum induced a flow of bile which was light yellow at first ("A" bile), but which later became darker and more viscid ("B" bile.) He assumed that the "B" bile came directly from the gall bladder, but this assumption has been disputed by some investigators.

Several investigators have studied the effect of magnesium sulphate upon sphincter resistance in animals.



Fig. 4. Diagrams illustrating the effect of five, ten and twenty per cent solutions of magnesium sulphate upon the sphincter of Oddi. The method of recording is the same as in Fig. 1.

McWhorter (6), Jacobson and Gydeson (7), Winkelstein and Aschner (8), Iwanaga (9), Shi (10) and others reported that it caused relaxation of the sphincter of dogs. Lueth (11) stated that five cubic centimeters of twenty-five per cent solution produced a temporary decrease in sphincter resistance with a return to the original level after one or one and one-half minutes. Instillation of twenty cubic centimeters

of the same solution resulted in either an increase or no change in intramural resistance. Puestow (12) stated that magnesium sulphate had an inconstant stimulating effect upon the duodenal musculature in dogs, but no evidence independent activity upon the orifice of the choledochus. Gantt and Volborth (13) observed that the introduction of magnesium sulphate solution into the duodenum of dogs was not followed by the expulsion of bile and that the drug did not have any constant effect upon the pressure within the gall bladder and bile ducts. Boyden and Birch (14, 15) noted that magnesium sulphate given by mouth or by duodenal tube to cats did not induce emptying of the gall bladder.

In one human subject, Ivy, Voegtlin and Greengard (16) apparently relieved spasm of the sphincter (which had been provoked by the intravenous injection of a secretin-cholecystokinin mixture) by the instillation of magnesium sulphate into the duodenum. Doubilet and Colp (17) and Best and Hicken (18) also reported sphincter relaxation following the administration of magnesium sulphate in man.

In our series of 42 observations magnesium sulphate produced sphincter relaxation 33 times. In the remaining 9 instances there was no change in three cases, an initial increase followed by a return to the original tonus level in five, and a prolonged sphincter contraction in one case. In 17 (71 per cent) of the 24 patients in whom measurements of sphincter resistance were made without interruption following the administration of magnesium sulphate, there was an initial increased resistance. The salt was administered by mouth in 6 and by duodenal tube in 11 of these 17 cases. It is apparent, therefore, that the sphincter relaxation often is preceded by a temporary increased intramural resistance. Ingestion or introduction into the duodenum of water alone or of saline solution does not produce this effect, and similar observations have been made by Doubilet and Colp (17.) These latter investigators (17) also observed the initial increased

sphincter resistance following the administration of magnesium sulphate.

There has been some question as to the effectiveness of the oral route of administration of magnesium sulphate as compared to duodenal instillation. Meltzer (4) stated that the salt was ineffective when given by mouth. Eppinger (19) also advised duodenal instillation of the drug. Dunn and Connell (20) disagreed, and stated that one would not expect any inactivating change in the magnesium sulphate solution to occur during its passage through the stomach. Best and Hicken (18) noted that this drug produced a relaxation of the sphincter (as judged by cholangiograms) when administered orally or intraduodenally. Our results indicate that the relaxing effect upon the sphincter is similar whether the drug be given by mouth or administered intraduodenally, and according to Boyden and Birch (14, 15), the same is true of the motor effect upon the human gall bladder. However, this relaxing effect is not great. It is less constant and weaker than the effect produced by amyl nitrite or by a fatty meal (21.) For example, the average maximum fall after a fatty meal of egg yolk and cream is approximately 7 cm. of saline solution pressure (22.)

## CONCLUSIONS

(1) Magnesium sulphate may produce any one of four types of effects upon the sphincter of the common bile duct. It may produce relaxation with or without an initial contraction, it may produce an initial contraction followed by a return to the original tonus level, or there may be no effect.

(2) The drug is equally effective in producing relaxation of the sphincter of Oddi whether administered orally or intraduodenally. Relaxation, however, is not constant and is considerably less than relaxation following the administration of amyl nitrite or ingestion of a fatty meal. The average maximum decrease in sphincter resistance in those cases showing relaxation following the administration of magnesium sulphate is slightly less than four centimeters of saline solution pressure.

## REFERENCES

1. Layne, J. A. and Bergh, G. S.: An Experimental Study of Pain in the Human Biliary Tract Induced by Spasm of the Sphincter of Oddi. *S. G. O.*, 70:18-24, Jan., 1940.
2. Mann, F. C.: The Function of the Gall Bladder. An Experimental Study. *New Orleans Med. Surg. J.*, 71:80-92, Aug., 1915.
3. Elman, R. and McMaster, P. D.: The Physiological Variations in Resistance to Bile Flow to the Intestine. *J. Exper. Med.*, 44:151-171, Aug., 1926.
4. Meltzer, S. J.: The Disturbance of the Law of Contrary Innervation as a Pathogenetic Factor in the Diseases of the Bile Ducts and the Gall Bladder. *Am. J. Med. Sci.*, 153:463-477, April, 1917.
5. Lyon, B. B. V.: Diagnosis and Treatment of Diseases of the Gall Bladder and Biliary Ducts. Preliminary Report on a New Method. *J. A. M. A.*, 73:980-982, Sept. 27, 1919.
6. McWhorter, G. L.: The Surgical Significance of the Common Bile-Duct Sphincter. *S. G. O.*, 32:124-130, Feb., 1921.
7. Jacobson, C. and Gydeson, C.: The Function of the Gall Bladder in Biliary Flow. *Arch. Surg.*, 5:374-394, Sept., 1922.
8. Winkelstein, A. and Aschner, P. W.: The Pressure Factors in the Biliary-Duct System of the Dog. *Am. J. Med. Sci.*, 168:812-819, Dec., 1924.
9. Iwanaga, Hitoo: Experimentelle Studien über den Mechanismus der Gallenausscheidung, insbesondere über die Funktion des Oddi'schen Sphinkters. *Mitt. a. d. med. Fch. d. k. Kyushu-Universität*, 10:1-60, 1925.
10. Shi, K.: The Influence of the Gall Bladder, Oddi's Muscle and the Duodenum Upon the Outflow of Bile. *Japan J. Gastroenterol.*, 5:26-30, April, 1933.
11. Lueth, H. C.: Studies on the Flow of Bile Into the Duodenum and the Existence of a Sphincter of Oddi. *Am. J. Physiol.*, 99:237-252, 1931.
12. Puestow, C. B.: The Discharge of Bile Into the Duodenum: An Experimental Study. *Arch. Surg.*, 23:1013-1029, 1931.
13. Gantt, W. H. and Volborth, G.: The Influence of Magnesium Sulphate on the Expulsion of Bile from the Gall Bladder. *J. Lab. and Clin. Med.*, 11:542-547, March, 1926.
14. Boyden, E. A. and Birch, C. L.: Emptying of Human Gall Bladder After Saline Cathartics. *Proc. Soc. Exper. Biol. and Med.*, 25:840-842, 1928.
15. Boyden, E. A. and Birch, C. L.: Reaction of Gall Bladder to Stimulation of Gastro-Intestinal Tract. 1. Response to Substances Injected Into the Duodenum. *Am. J. Physiol.*, 92:27-309, March, 1930.
16. Ivy, A. C., Voegtlin, W. L. and Greengard, H.: The Physiology of the Common Bile Duct: A Singular Observation. *J. A. M. A.*, 100:1319-1320, 1933.
17. Doubilet, H. and Colp, R.: Resistance of the Sphincter of Oddi in the Human. *S. G. O.*, 64:622-633, March, 1937.
18. Best, R. R. and Hicken, N. F.: The Therapeutic Value of Glycerol Trinitrate in Biliary Colic and in the Post-Operative Phase of Biliary Tract Disease. *Am. J. Surg.*, 30:533-537, March, 1935.
19. Eppinger, H.: Die Leberkrankheiten. Vienna, Julius Springer, 1937.
20. Dunn, A. D. and Connell, K.: Report of a Case of Hepatoduodenostomy with Some Observations on the Lyon-Meltzer Method of Biliary Drainage. *J. A. M. A.*, 77:1093-1096, Oct. 1, 1921.
21. Bergh, G. S.: The Sphincter Mechanism of the Common Bile Duct in Human Subjects: Its Reactions to Certain Types of Stimulation. Doctor's Thesis, University of Minnesota, 1940.
22. Bergh, G. S.: The Effect of Food Upon the Sphincter of Oddi in Human Subjects. *Am. J. Dig. Dis.*, 1:40, Jan., 1942.



# Is the Beneficial Effect of Urine Extracts on Mann-Williamson Ulcers due to the Gastric Secretory Depressant in Urine?\*

By

DAVID J. SANDWEISS, M.D.

and

M. H. F. FRIEDMAN, Ph.D.†

DETROIT, MICHIGAN

THE chief factors involved in the production and maintenance of chronicity of Mann-Williamson ulcers appear to be: (a) a nutritional disturbance as a result of shunting bile and pancreatic and duodenal juices to a point low in the ileum; (b) mechanical stress due to either spasm of the jejunum or forcible ejection of gastric contents against the jejunal mucosa; (c) the specific susceptibility of the jejunal mucosa and (d) the irritant action of unneutralized gastric contents on the unprotected jejunal mucosa. Of these four factors, the role of the unneutralized gastric secretion has been emphasized most, and, indeed, some workers consider it the *sine qua non* of ulcer.

Previously we have shown: (a) that extracts of urine of pregnant women and normal women have a prophylactic and therapeutic effect against these Mann-Williamson ulcers (1, 2, 3); (b) that urine contains a gastric secretory depressant (4, 5, 6.) The question naturally arose whether the prophylactic and therapeutic effects obtained with urine extracts in Mann-Williamson dogs were due to depression of gastric secretion.

In previous communications (2, 3, 7) we noted that the protective action of pregnancy urine and normal female urine extracts against Mann-Williamson ulcers is probably not due to depression of gastric secretion. We noted that although daily subcutaneous injections of these extracts in doses of 1 and 5 mg. (70 and 350 cc. of urine) have a definite prophylactic and therapeutic effect against Mann-Williamson ulcers, they do not decrease the gastric secretory response to a meal when injected daily in normal dogs over a long period of time—even as long as 157 consecutive days (2.)

In the present paper we report the following two additional series of experiments bearing on the same subject:

(1) Two gastric fistula dogs received subcutaneous injections of 2 mg. of normal female urine extract (representing approximately 150 cc. urine) daily for a period of 45 days. Gastric acidity determinations were made at intervals before, during and after the period of treatment. Histamine was used as the gastric secretory stimulant. Samples of gastric juice were collected every 15 minutes for a period of one hour, and titrated in the usual manner for free and total acids. The total output of free acid was determined by multiplying the volume of juice secreted (in cubic centimeters) by the concentration of free acid. The

results are depicted in Graph 1. It will be seen that the total output of free hydrochloric acid was not depressed during the period of the experiment; neither was the concentration of free acid or total acid affected even after 45 daily subcutaneous injections of the extract.

(2) Gastric analyses were performed on normal dogs, control (untreated) Mann-Williamson dogs and on Mann-Williamson dogs treated with extracts prepared from urine of pregnant women, normal women and urine from patients having active symptoms of duodenal ulcer. All dogs were fasted 24 hours. Histamine and beef-broth were used as test meals. Samples of juice were aspirated 30 to 45 minutes after the test meal; the free and total acidities were determined by the usual method of titration. It will be noted from Tables I and II that: (a) In the series of animals with histamine as the gastric secretory stimulant (see Table I) the range in the acidities of the various series of dogs are approximately the same. (b) In the series of animals with beef-broth as the gastric secretory stimulant (see Table II) a similar range of acidities was obtained in the various series of animals.

## DISCUSSION

Data published elsewhere (1, 2, 3, 12) indicate that extracts from urine of pregnant women and normal women have a prophylactic and therapeutic effect against experimental ulcers in dogs produced by the Mann-Williamson operative technique, while extracts prepared from urine of patients having active symptoms of duodenal ulcer have little if any such effect. As urine contains a gastric secretory depressant, gastric secretory studies were performed on normal dogs, fistula and pouch dogs, as well as on our Mann-Williamson dogs that have been treated with the various extracts. From the above secretion studies it appears that subcutaneous injections of the extracts (in doses found effective against Mann-Williamson ulcers) do not depress gastric secretion, either in concentration of acid or total output of acid. This holds true for all urine extracts so far studied, although there is a marked difference between ulcer urine extracts and pregnancy and normal female urine extracts on Mann-Williamson ulcers. The former (ulcer urine extracts) have little if any beneficial effect, while the latter (pregnancy and normal female urine extracts) have a definite prophylactic and therapeutic effect on Mann-Williamson ulcers.

Other groups (8, 9, 10) as well as our group (4, 5, 6) have shown that urine contains a gastric secretory depressant. Why, then, was not gastric secretion inhibited in our Mann-Williamson dogs that have been treated over a long period of time (even as long as

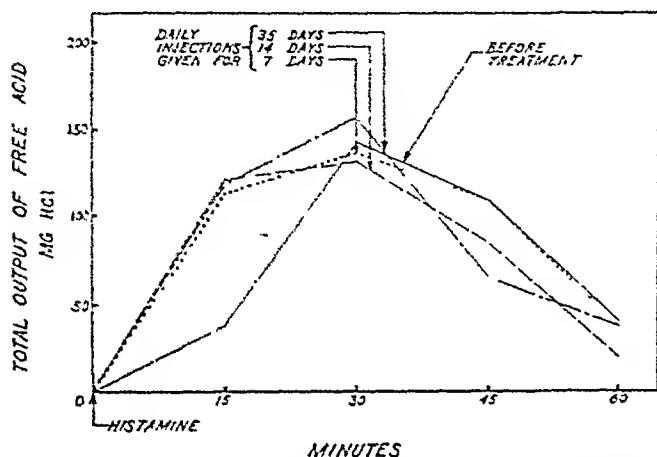
\*From the Laboratories of Experimental Surgery at Harper Hospital, Detroit, Michigan, and Department of Physiology, Wayne University, College of Medicine, Detroit, Mich.

†Now at the Jefferson Medical College, Philadelphia.

Aided by grants from the Mendelson Fund and Parke Davis & Company.

Submitted August 1, 1941.

three years)? In the present state of preparation, the gastric secretory depressant in urine extract appears to be effective in 1 to 5 mg. doses (70 to 350 cc. urine) *only when administered by vein*. In our Mann-Williamson dogs, we have used small doses of both pregnancy and normal urine extracts *subcutaneously* or *intramuscularly* but *not intravenously*. We have found that very much larger doses of the extract (10-15 times the effective intravenous dose) would be needed to exert an inhibitory effect on secretion when given either subcutaneously or intramuscularly. (We are now treating a series of Mann-Williamson dogs with large doses subcutaneously to depress secretion.) Likewise, Ivy et al (11) have found that pregnancy urine extract (Antuitrin-S) in the dosage used by us (1 to 5 cc. or 100-500 rat units) has no effect on gastric secretion



Graph 1. Total output of free acid in a gastric fistula dog receiving daily 2 mgms. urine extract subcutaneously (representing 140 cc. urine.) Note that this dose, which is effective subcutaneously in protecting the Mann-Williamson dog against ulcers, does not depress gastric secretion when given by this route for as long as 45 consecutive days. (Only first three post treatment determinations shown in graph.)

when given subcutaneously but that 10 to 20 cc. daily (1000 to 2000 rat units) definitely decreased the acid output of 2 gastric pouch dogs.

Interestingly enough, the extracts from urine of ulcer patients when administered intravenously also depress gastric secretion in the dog. However, they have little, if any, effect on Mann-Williamson ulcers when given subcutaneously.

It is therefore evident that the prophylactic and therapeutic effects of pregnancy and normal female urine extracts against experimental Mann-Williamson ulcers (small doses administered subcutaneously) were quite independent of any effect on gastric secretion.\*

We do not yet know what factor in normal female and pregnancy urine extract is responsible for the prophylactic and therapeutic action. We know, however, that the beneficial effect was obtained independently of the gastric secretory depressant and, what is more important, that healing of these experimental ulcers can take place in the presence of an essentially unaltered gastric acid juice.

\*In this connection the question naturally might be asked what effect intravenous administration of the extracts has on Mann-Williamson ulcers. Theoretically, by depressing gastric secretion Mann-Williamson ulcers should be prevented. We treated six Mann-Williamson dogs intravenously. The results, however, were indeterminate since we found it difficult to administer the extract by this route daily over a long period of time. This study will be repeated.

TABLE I  
Concentration of free acid—Clinical units  
*Histamine*

|   | Number Dogs | Number Tests | Average Concentration Free Acid |
|---|-------------|--------------|---------------------------------|
| Normal dogs                                 | 5           | 5            | 66.1                            |
| Mann-Williamson dogs (No treatment-control) | 7           | 8            | 72.5                            |
| Mann-Williamson dogs treated with           |             |              |                                 |
| (a) Urine from pregnant women               | 2           | 2            | 80.9                            |
| (b) Urine from normal women                 | 2           | 4            | 61.8                            |
| (c) Urine from normal men                   | 5           | 5            | 96.5                            |
| (d) Urine from ulcer patients               | 3           | 4            | 61.9                            |

Our evidence at present points to urine extract as exerting its beneficial effect through stimulation of active fibroblastic proliferation and epithelialization of the ulcer (12.) Apparently this process can take place in the presence of an unaltered acid juice.

### SUMMARY

1. When histamine and beef-broth were used as gastric secretory stimulants, the range in the acidities were the same in both the treated and untreated Mann-Williamson dogs. The Mann-Williamson dogs that benefited by treatment (that lived longer than the maximum survival time of our control dogs—as long as two and three years following the operation) showed approximately the same concentration of acid as did our control (untreated) dogs. It therefore appears that the prophylactic and therapeutic effect against Mann-Williamson ulcers obtained with the extracts from urine of pregnant and normal women was not due to the inhibition of acid by the gastric secretory depressant in urine.

2. Apparently pregnancy urine extracts and normal female urine extracts exert a beneficial effect through stimulation of active fibroblastic proliferation and epithelialization of the ulcer. This process can occur in the presence of an unaltered gastric acid juice. Apparently pregnancy urine extracts and normal female urine extracts exert a beneficial effect through stimulation of active fibroblastic proliferation and epithelialization of the ulcer. This process can occur in the presence of an unaltered gastric acid juice.

TABLE II  
Concentration of free acid—Clinical units  
*Beef broth meal*

|   | Number Dogs | Number Tests | Average Concentration Free Acid |
|---|-------------|--------------|---------------------------------|
| Mann-Williamson dogs (No treatment-control) | 5           | 5            | 57.7                            |
| Mann-Williamson dogs treated with           |             |              |                                 |
| (a) Urine from pregnant women               | 2           | 2            | 57.7                            |
| (b) Urine from normal women                 | 2           | 3            | 43.3                            |
| (c) Urine from ulcer patients               | 2           | 3            | 41.3                            |

## REFERENCES

1. Sandweiss, D. J., Saltzstein, H. C. and Farbman, A. A.: The Prevention or Healing of Experimental Ulcer in Mann-Williamson Dogs with the Anterior-Pituitary-like Hormone (Antuitrin-S.) *Am. J. Dig. Dis.*, Vol. 5, No. 1, pp. 24-30, March, 1938.
2. Sandweiss, D. J., Saltzstein, H. C. and Farbman, A. A.: The Relation of Sex Hormones to Peptic Ulcer. *Am. J. Dig. Dis.*, Vol. 6, No. 1, pp. 6-12, March, 1939.
3. Sandweiss, D. J., Sugarman, M. H. and Friedman, M. H. F., Saltzstein, H. C. and Farbman, A. A.: The Effect of Urine Extracts on Peptic Ulcer. An Experimental and Clinical Study. *Am. J. Dig. Dis.*, Vol. 8, No. 10, pp. 371-382, Oct., 1941.
4. See 2, page 11.
5. Friedman, M. H. F., Rechnagel, R. O., Sandweiss, D. J. and Patterson, T. L.: Inhibitory Effect of Urine Extracts on Gastric Secretion. *Proc. Soc. Exp. Biol. and Med.*, 41:569, June, 1939.
6. Friedman, M. H. F. and Sandweiss, D. J.: The Gastric Secretory Depressant in Urine. *Am. J. Dig. Dis.*, Vol. 8, No. 10, pp. 366-371, Oct., 1941.
7. Sandweiss, D. J. and Friedman, M. H. F.: The Use of Urine Extracts in the Treatment of Ulcer. *Am. J. Dig. Dis.*, 7:50, Jan., 1940.
8. Gray, J. S., Wiczorowski, E. and Ivy, A. C.: Inhibition of Gastric Secretion by Extracts of Normal Male Urine. *Science*, 89:489, May, 1939.
9. Necheles, H., Hanke, M. E. and Fantl, E.: Preparation and Assay of Inhibitor of Gastric Secretion and Motility from Normal Human Urine. *Proc. Soc. Exp. Biol. and Med.*, 42:619, Nov., 1939.
10. Hanke, N. E.: A Crystalline Protein from Normal Urine. *Proc. Am. Soc. Biol. Chem.*, p. 40, March 13, 1940.
11. Culmer, C. U., Atkinson, A. J. and Ivy, A. C.: Depression of Gastric Secretion by Anterior Pituitary-like Fraction of Pregnancy Urine. *Endocrinology*, 24:631, May, 1939.
12. Weaver, D. C., Sandweiss, D. J., Saltzstein, H. C., Farbman, A. A. and Sanders, A. W.: The Effect of Urine Extracts on the Prevention and Healing of Experimental Ulcers in Dogs. *Am. J. Clin. Path.* In press.

## On the Explanation of the Urobilinuria Present in Cases of Hematoma and a New View on the Origin of Urobilinogen from Bile Pigment

By

J. W. G. TEN BOKKEL HINNINK, M.D.

TIEL, HOLLAND

MANY clinicians have observed the presence of urobilinuria in cases of hematoma due to various causes. According to the enterogenous theory, it has to be assumed that, owing to the resorption of the quantity of bile pigment formed in the hematoma (1), the liver excretes a little more bilirubin than usual into the intestine, and consequently a slightly greater quantity of urobilinogen is formed. After the resorption of this slight surplus of urobilinogen from the intestine, the liver is unable to assimilate it and allows part of it to pass into the general circulation

in order to re-investigate this subject using human and animal experimentation.

Is it possible to cause urobilinuria by feeding bile to a human patient with a biliary fistula? If we assume that urobilinuria arises when the quantity of bile pigment secreted into the intestine is slightly above the normal, it should be possible to cause urobilinuria by the administration of bile orally. A patient with a cholecystectomy and a drain in the ductus hepaticus was used as a source of bile. Urobilinogen was determined in the feces and urine by

TABLE I

The effect of oral administration of whole bile on the urobilinogen content of urine and feces

| Administration of 600 cc. of Whole Bile Containing 700 mg. Bilirubin |                   |                             |             |                  |        | Administration of 3000 cc. of Bile Containing 2660 mg. Bilirubin |                   |                             |             |                  |        |
|--|-------------------|-----------------------------|-------------|------------------|--------|--|-------------------|-----------------------------|-------------|------------------|--------|
| Days   | Regimen           | Average Urobilinogen Output |             |                  |        | Days   | Regimen           | Average Urobilinogen Output |             |                  |        |
|  |                   | Urine                       |             | Feces            |        |  |                   | Urine                       |             | Feces            |        |
|  |                   | Mg./24 Hrs.                 | Mg./24 Hrs. | Total mg. Excess | % Rec. |  |                   | Mg./24 Hrs.                 | Mg./24 Hrs. | Total mg. Excess | % Rec. |
| 9  | Control           | 0.7                         | 142         |                  |        | 4  | Control           | 0.6                         | 140         |                  |        |
| 3  | Bile Feeding      | 0.9                         | 175         | 168              | 23     | 7  | Bile Feeding      | 0.9                         | 205         | 669              | 24     |
| 9  | Post-Bile Feeding | 0.9                         | 143         |                  |        | 7  | Post-Bile Feeding | 0.7                         | 142         |                  |        |

from which it is removed by the kidneys. Thus we have to assume a relative insufficiency of the liver and to suppose that the liver is only capable of preventing the normal quantity of urobilinogen from passing into the general circulation, but fails when the supply is a little above normal. In this respect the liver would, according to this theory, act to the maximum of its capacity when it functions normally. This explanation for the occurrence of urobilinuria in the presence of a hematoma seemed erroneous; therefore, it was de-

Terwen's modification of the Ehrlich's reaction. Human bile, free from urobilin and urobilinogen, was fed orally to a normal subject during the test period. In one case 700 mg. of bilirubin was administered in 600 cc. of bile over a period of 3 days, while in another instance as much as 2660 mg. in 3000 cc. were fed over a period of 7 days. As Table I shows, a definite urobilinuria did not result, and only approximately 25 per cent of the available bilirubin was recovered as fecal urobilinogen. Consequently, in healthy people, it is impossible to cause urobilinuria by the administration of human bile even in large quantities.

TABLE II

*The effect of oral administration of indirect-reaction bilirubin on urobilinogen output*

| Administration of 1000 cc. of Horse Serum Containing 50 mg. of Indirect Bilirubin |                    |   |       | Administration of 575 cc. Horse Serum Containing 43 mg. Indirect Bilirubin |                    |   |       |
|---|--------------------|---|-------|--|--------------------|---|-------|
|   |                    | Average Urobilinogen Output mg./24 Hrs. |       |  |                    | Average Urobilinogen Output mg./24 Hrs. |       |
| Days  | Regimen            | Urine                                   | Feces | Days   | Regimen            | Urine                                   | Feces |
| 4   | Control            | 0.6                                     | 153   | 1  | Control            | 0.7                                     | 150   |
| 2   | Serum Feeding      | 0.55                                    | 131   | 1  | Serum Feeding      | 0.6                                     | 125   |
| 7   | Post-Serum Feeding | 0.6                                     | 151   | 5  | Post-Serum Feeding | 0.7                                     | 147   |

Similar results were obtained when 13 mg. of indirect bilirubin in the serum of a horse with hemolytic anemia was given orally.

*The effect of feeding indirectly reacting bilirubin in producing urobilinuria.* Since the bilirubin formed in hematomas is of the indirectly-reacting type in contrast to the directly-reacting bilirubin present in bile, the next step was to determine the effect of feeding indirect bilirubin on the urobilinogen output of a cholecystectomized patient. The indirect bilirubin was obtained by injecting a horse with phenylhydrazine, and then using the serum which contained 10-12 units of bilirubin. The oral administration of small amounts (43 or 50 mg.) of indirectly-reacting bilirubin caused no change in the urine and fecal urobilinogen. The results are shown in Table II.

*Urobilinogen excretion in patients with a hematoma.* Because of this second experimental failure, it was obvious that the only way to further the solution of the problem was to determine the urobilinogen excretion in the presence of hematoma itself. Two human subjects with a large hematoma (ranging from 0.3-1.0 liter) due to a fracture were observed during

the period of resorption and the period immediately following, so as to establish control urobilinogen outputs in the urine and feces (Table III.) The total excretion of urobilinogen in the feces, in the first case during the 28-day period of resorption of the hematoma, amounted to 5956 mg., during which time there was no urobilinuria, since the hematoma apparently was not large enough. This represented a surplus excretion in the feces of 2156 mg. over that of the control period; the average daily output was 136 mg. per day. In the second case, the surplus excretion of urobilinogen due to the breakdown of the hematoma over a period of 30 days amounted to 5786 mg. (10227-4441 = 5786 mg.) Urobilinuria occurred in a moderate degree for six days, immediately before the maximum excretion of fecal urobilinogen was obtained.

100 gm. of blood contains 14 gm. of hemoglobin, of which 4.47 per cent, or 623.8 mg. is hematin. From 604 gm. of hematin, 584 gm. of bilirubin may be formed, and from this 592 gm. of urobilinogen may arise. A simple calculation will show that from 100 gm. of blood, a maximum of 611 mg. of urobilinogen may be formed. The surplus in the first case (Table III) was 2156 mg., which must have come from 350 gm. of blood; in the second case 5786 mg., which must have come from 950 gm. of blood. Thus, the weight estimated by inspection corresponds well with the

TABLE III

*The excretion of urobilinogen in the urine and feces in a patient with fracture of the humerus and femur with hematoma*

| Urobilinogen |                    |                    | Urobilinogen |                    |                    |
|--------------|--------------------|--------------------|--------------|--------------------|--------------------|
| Day Case 1*  | Urine Ave./Day Mg. | Feces Ave./Day Mg. | Day Case 2** | Urine Ave./Day Mg. | Feces Ave./Day Mg. |
| 1-3          | 5.5                | 137                | 1-5          | 0.8                | 191                |
| 4-6          | 0.6                | 261                | 6-10         | 1.8                | 484                |
| 9-13         | 0.3                | 314                | 11-15        | 1.1                | 568                |
| 14-18        | 0.3                | 203                | 16-20        | 0.5                | 279                |
| 19-23        | 0.5                | 186                | 21-25        | 0.5                | 222                |
| 24-28        | 0.5                | 145                | 26-30        | 0.5                | 282                |
| 29-33*       | 0.5                | 136                | 31-40        | —                  | 153                |
| 34-39        | 1.1                | 135.7              | 41-50        | —                  | 152                |

\*On 29th day hematoma (0.3-0.4 liter) was entirely reabsorbed (fracture of humerus.)

\*\*On 30th day hematoma (0.75-1.0 liter) was entirely reabsorbed (fracture of femur.)

Case 1. Total urobilinogen in feces for 28 days = 5956 mg.  
Normal urobilinogen in feces/day for 28 days = 3800 mg.

Surplus due to hematoma = 2156 mg.  
Case 2. Total urobilinogen in feces for 30 days = 10227 mg.  
Normal urobilinogen in feces/day for 30 days = 4441 mg.

Surplus due to hematoma = 5786 mg.

TABLE IV

*The excretion of urobilinogen in the urine and feces in the case of an artificial hematoma (200 cc.)*

| Urobilinogen |                    |                    |
|--------------|--------------------|--------------------|
| Day          | Urine Ave./Day Mg. | Feces Ave./Day Mg. |
| 1-4          | —                  | 146                |
| 5-11         | 0.5                | 146*               |
| 12-16        | 0.8                | 151                |
| 17-21        | 1.0                | 305                |
| 22-26        | 0.4                | 176**              |
| 27-35        | 0.5                | 155                |
| 36-43        | —                  | 146                |

\*Blood injected on 10th day.

\*\*Mostly absorbed on 26th day; yellow color practically gone on 35th day.

surplus of fecal urobilinogen found. It should be added that several persons estimated by inspection the original size of the hematoma.

In order to control more accurately the preceding observations, a known quantity (200 cc.) of a subject's blood taken from a vein and mixed with sodium citrate was injected subcutaneously. The normal urobilinogen excretion had been determined beforehand. The averaged data are shown in Table IV. The surplus obtained from the feces amounted to 1070 mg. Since 1220 mg. of urobilinogen is the maximum obtainable from 200 cc. of blood, the surplus represented a recovery of 88 per cent, which is good considering the nature of the experiment. The urobilinuria is negligible. (It would be of interest to determine in those animals in which urobilinogen is not excreted whether extrahepatic formation of bilirubin is absent, and if so, whether urobilinogen is formed in the intestine of such an animal when an artificial hematoma is formed.)

Thus, it can be seen that the bilirubin formed extra-hepatically is quantitatively converted in the intestine to urobilinogen and excreted. This is in direct contrast to the results obtained when indirect bilirubin or whole bile was administered orally. In the former experiment only 25 per cent of the available bilirubin was recovered as excreted urobilinogen.

The only plausible explanation for this difference is that urobilinogen originates only from the bilirubin formed extra-hepatically, whereas the bilirubin formed by the liver is not converted into urobilinogen, but probably into some other pigment such as copronigrin (2), which can be found in feces in much larger quantities than urobilinogen. Therefore, it must be assumed that in bile there are two types of bilirubin: one which is formed extra-hepatically and is not changed into the direct bilirubin by the liver, but is the one which is converted into urobilinogen in the intestine; and the other, the direct reacting bilirubin which is excreted as such but is not converted into urobilinogen.

To examine this concept two additional experiments were performed. In one, bile containing only the directly-reacting bilirubin was administered by stomach tube to obstructive-jaundiced dogs. The other investigation consisted of *in vitro* studies to determine the effect of intestinal bacteria on both indirectly and directly reacting bilirubin.

*The administration of directly and indirectly reacting bilirubin to dogs with obstructive jaundice.* The dogs were prepared by doubly ligating and cutting the common ducts. It was found that the feces of these dogs always contained a small amount of urobilinogen, probably due to the intestinal bleeding found with the exclusion of bile from the intestine (Vitamin K was not known at the time of these experiments.) Further, the urine of these dogs also contained indirect bilirubin, in spite of the fact that the kidney threshold for this type of bilirubin is very high. Wespi (3) believes that this is due to the influence of the bile salts in the blood which affects the capillary permeability of the glomeruli.

These dogs were fed urine containing only directly-reacting bilirubin. It was found that by shaking urine 4 or 5 times with chloroform the indirectly reacting bilirubin was practically entirely removed, leaving only the directly reacting bilirubin. This procedure cannot, however, be utilized for the quantitative separation of these pigments in bile.

When 61 mg. of direct reacting bilirubin in urine was administered by stomach tube over a period of 5 days, there was no change in fecal urobilinogen over that of the control period. When various amounts of indirectly reacting bilirubin ranging from 10-65 mg. was administered, there was an appreciable increase in the fecal urobilinogen (Table V.) There was no urobilinuria. Due to the presence of urobilinogen in the feces it is difficult to compute accurately the quantity derived from the administered pigment, but these experiments show that urobilinogen is formed

TABLE V

*The effect of oral and rectal administration of indirect and direct-reacting bilirubin on urobilinogen output in obstructive-jaundiced dogs*

| Days | Regimen                                 | Av. Output of Urobilinogen<br>Mg./24 Hrs. |       |
|------|---|---|-------|
|      |   | Urine                                     | Feces |
|      | Control (pre- and post-feeding periods) | 0.1-0.2                                   | 0.4   |
| 5    | 61 mg. (total) direct bil.              | 0.1-0.2                                   | 0.3   |
| 3    | 27 mg. (total) indirect bil.            | 0.3                                       | 1.3   |
| 5    | 65 mg. (total) indirect bil.            | 0.51                                      | 2.2   |
| 3    | 15 mg. (total) direct bil.              | trace                                     | 0.2   |
| 3    | 10 mg. (total) indirect bil.            | 0.2                                       | 1.62  |

from the indirect bilirubin, but not from the directly reacting bilirubin.

From the foregoing results, and the results of other experiments involving the use of the serum of patients with obstructive jaundice and the administration of directly and indirectly reacting bilirubin rectally to avoid changes that the acidity of the gastric juice might induce when bilirubin is given orally, it is certain that urobilinogen arises from indirectly reacting bilirubin but not from directly reacting bilirubin. However, the results are not so striking as anticipated. Indirect bilirubin was not recovered quantitatively as urobilinogen, which may have been due to the action of gastric juice. The same was true of the results of rectal administration, which was attended by great difficulties in the experimental animal. It would be desirable to perform a protracted experiment in a patient with complete obstructive jaundice and to introduce the bilirubin into the duodenum by an Einhorn tube. Such a patient was not available.

*The effect of bacteria on directly and indirectly reacting bilirubin.* To substantiate the preceding finding, *in vitro* studies were made in which direct (from urine

of a patient) and indirect reacting (horse serum, hemolytic jaundice) bilirubin were incubated at 37° C. with a small amount of urobilinogen-free feces, obtained from an obstructive jaundice patient. After 7 days of incubation no urobilinogen or urobilin was found in the reports containing the direct reacting bilirubin, while approximately all the indirect reacting bilirubin was converted quantitatively into urobilinogen in 33 hours. In addition studies were made in which the bacteria were incubated with the sera obtained from patients with complete obstructive jaundice. Table VI shows that only the indirect-reacting bilirubin in the serum was quantitatively converted into urobilinogen.

Kammerer and Miller (9) found that intestinal bacteria would convert crystalline indirectly reacting bilirubin into urobilinogen; they did not study the effect of bacteria on directly-reacting bilirubin.

### DISCUSSION

Both by experimental and *in vitro* studies, evidence has been presented which indicates that urobilinogen

TABLE VI

*The conversion of direct and indirect-reacting bilirubin into urobilinogen—in vitro studies*

| Serum I   |                  | Serum II   |                  |
|---|------------------|--|------------------|
| Direct Bilirubin = 17 Mg.<br>Indirect Bilirubin = 3 Mg. |                  | Indirect Bilirubin = 15 Mg.<br>Direct Bilirubin = 15 Mg. |                  |
| Hours   | Mg. Urobilinogen | Hours  | Mg. Urobilinogen |
| 0   | —                | 0  | —                |
| 17  | 0.07             | 43   | 1.39             |
| 37  | 2.1              | 68   | 1.48             |
| 59  | 3.0              | 90   | 1.48             |
| 83  | 3.0              | 140  | 1.45             |
| 100   | 2.9              |  |                  |

is formed only from the indirectly reacting bilirubin which originates extra-hepatically. When whole bile is fed only 25 per cent of the total pigment in bile is recovered in the feces as urobilinogen. Therefore, since bile contains mostly directly reacting bilirubin, approximately 25 per cent of the bile pigment must be formed extrahepatically. Experimental studies on human and canine subjects, as well as *in vitro* studies, showed no urobilinogen formation from directly reacting bilirubin. My original supposition, that the urobilinuria associated with a hematoma is due to the formation of a "foreign" urobilinogen which is not removed by the liver, appears to be wrong. The urobilinuria is due to conversion of the extra-hepatic-indirect bilirubin into urobilinogen in the intestine. Heilmeyer and Krebs (4) found that indirectly reacting crystalline bilirubin given orally could quantitatively be recovered from the feces as urobilinogen. Also, on injecting laked blood, both Kuhl (5) and Heilmeyer (6) obtained a quantitative excretion of urobilinogen equivalent to the amount of hemoglobin. I have obtained similar results by producing an arti-

ficial hematoma in a subject when 200 cc. of citrated blood was injected subcutaneously. Clinically, it has been observed that whenever the formation of extra-hepatic bilirubin is increased or decreased, there is an associated change in the urobilinogen output.

Lichtenstein and Landberg (7) reported a marked decrease in urobilinogen excretion after extirpation of the spleen in essential thrombocytopenia. Singer (8) found similar results in dogs. In hemolytic jaundice the excretion of urobilinogen is considerable, but returns to normal upon removal of the spleen. In a patient with pernicious anemia, I was able to find, like Heilmeyer, a certain parallelism between the urobilinogen excretion and the amount of indirectly reacting bilirubin present in the blood. Thus it should be possible to determine the amount of blood which is broken down extra-hepatically by determining the urobilinogen excretion. The principle organs in which the formation of extra-hepatic bilirubin occurs are the spleen, bone-marrow, and lymph glands.

The original object of this research, to find a cause of urobilinuria in cases of hematoma, has, I think, been attained. This urobilinuria is fully explained by the large quantities of urobilinogen formed in the intestine as a result of the reabsorption of the blood and an increase in elimination of indirect bilirubin in the bile. The error in the reasoning which appeared to render the enterogenous theory difficult to accept is now clear. The starting point is the current supposition that the quantity of bilirubin formed in hematoma in relation to that normally in the bile is relatively insignificant (1, 11.) This is really not the case, since all the hemoglobin from a hematoma is changed to indirectly reacting bilirubin which is quantitatively changed to urobilinogen in the intestine. Owing to the rapid absorption of bilirubin, only small quantities are found in the hematoma. When one observes the relatively large quantities of urobilinogen in the feces of a patient with a large hematoma, it is not surprising that a normal liver will allow some to pass into the general circulation to be excreted in the urine. From the observations made, urobilinuria in cases of hematoma is not at variance with the enterogenous theory of urobilinogen formation, and all other explanatory theories are superfluous (11.)

The idea that indirectly reacting or extrahepatically formed bilirubin is excreted by the liver as such and that it amounts normally in man to only about 25 per cent of the total bile bilirubin, and that the remainder, about 75 per cent of bilirubin is formed by the liver is contrary to the conclusion of the experiments of Mann, Sheard, Bollman and Baldes (12.) These authors on the basis of the results of ingenious experiments conclude that most of the bilirubin is formed extrahepatically. However, the experiments and certain conclusions drawn from them may be criticized. After anesthesia and extensive operation it may be true that much bilirubin is formed extrahepatically, so that the hyperbilirubinemia occurs as rapidly as after common duct obstruction with cholecystectomy. The comparison is defective in that in the latter case



bile pigment may pass into the urine and tissues quite rapidly; also some pigment can pass into the obstructed duct system, which cannot occur when the liver is out. Also, obstruction may decrease the rate of intrahepatic formation of bilirubin which would tend to alter the picture.

A closer and more exact study will have to settle whether the share of the liver in cases of increased hemolysis is normal or less than normal. In such cases, pernicious anemia and hemolytic icterus, large quantities of urobilinogen are excreted which obviously come from the increased extrahepatically formed bilirubin. These quantities can be so great that one can hardly assume that the quantity of hemoglobin changed by the liver should have been augmented as well. Under physiological conditions it appears to have been established that extrahepatically formed bilirubin is excreted as such in the bile and can be recovered in the feces as urobilinogen. This quantity normally amounts to about 25 per cent of the total quantity of bilirubin in bile. It follows that the remaining 75 per cent of the bilirubin in bile originates in the liver.

### SUMMARY

The urobilinuria in cases of hematoma is currently explained as being due to the increase in bilirubin excretion into the intestine with an increased production and absorption of urobilinogen to such an extent that the liver cannot remove it from the portal blood. This seemed to be erroneous because it assumes that the liver, contrary to other organs, normally acts to its full capacity in regard to the removal of urobilinogen. It was found that urobilinuria does not occur when large quantities of bile are given orally to healthy human subjects, and that only 25 per cent of the bilirubin is recovered in the feces as urobilinogen. The oral administration of small amounts (43 or 50 mg.) of indirect bilirubin did not cause urobilinuria, which should have occurred if indirect bilirubin is changed in the intestine or in the hematoma to a type of urobilinogen that is difficult for the liver to remove. On the basis of the results, if a large quantity of indirectly reacting bilirubin were to be introduced into the duodenum, sufficient urobilinogen should be formed and absorbed to overtax the capacity of the normal liver to remove it from the portal blood, and a urobilinuria should result. On studying urobilinogen excretion in the urine and feces of persons with natural and artificial hematomas, it was found that 88 per cent of the theoretical yield of urobilinogen from the hemoglobin in the hematoma could be recovered in the feces, which represents an excellent degree of recovery. It was also found that some urobilinuria occurs in the presence of large hematomas when large quantities of urobilinogen are formed in the intestinal canal—such large quantities that the liver cannot remove all that is absorbed. Thus, it may be concluded that the extrahepatically formed indirectly reacting bilirubin from a hematoma is changed into urobilinogen in the intestine.

Why, then, is only 25 per cent of the bilirubin in human bile, fed orally, converted into urobilinogen in the intestine? It appears logical to assume that only extrahepatically formed bilirubin (indirectly reacting) is changed into urobilinogen in the intestine, and that intrahepatically formed bilirubin (directly reacting) is not changed into urobilinogen. If this is true then 25 per cent of the bilirubin in human bile is extrahepatically formed and 75 per cent is intrahepatically formed. The former is converted to urobilinogen and the quantity is too small to overtax the liver; the latter is probably changed to copronigrin. When blood is being excessively destroyed, then more indirectly reacting or extrahepatically formed bilirubin is excreted in the bile, which results in the formation of a large amount of urobilinogen, some of which passes through the liver.

To test this assumption, directly and indirectly reacting bilirubin was administered to dogs with total obstruction of the common bile duct. The results, though the experimental methods were not ideal, indicated that indirectly reacting bilirubin yields urobilinogen, whereas directly reacting bilirubin does not. Further, when directly and indirectly reacting bilirubin is incubated with intestinal bacteria, urobilinogen is produced from indirectly reacting or extrahepatically formed bilirubin but not from directly reacting bilirubin.

### CONCLUSION

1. Extra-hepatically formed bilirubin is excreted as such in the bile and is not changed normally into directly reacting bilirubin by the liver.
2. Urobilinogen is only produced from extrahepatically formed or indirectly reacting bilirubin.
3. The directly reacting bilirubin formed by the liver is not changed into urobilinogen.
4. The daily excretion of urobilinogen is an accurate measure of the quantity of red blood cells which is being destroyed extrahepatically, this is true under normal conditions and in patients with increased hemolysis.
5. The excretion of urobilinogen cannot be used as a criterion of the total destruction of erythrocytes, since the extent to which the liver is concerned is not taken into account. In the presence of increased hemolysis, only the extrahepatic destruction of erythrocytes is presumably increased and the part of the pigment destroyed by the liver probably remains normal.

### REFERENCES

1. Hyman, A. and Draz, A. A.: Die Gallenfarbstoffe im Blute. London, von Decker, 1922.
2. Watson, C. J.: *Hoppe-Seyler's Ztschr. f. Physiol. Chem.*, 1923, Bd. 204, 1922, Bd. 224, 1923, Bd. 225, 1924, 226.
3. Wessly, H. J.: *Klin. Wochenschr.*, 1923.
4. Heilmeyer, L. and Kohn: *Ztschr. f. Physiol. Chem.*, 1924.
5. Kohn: *Arch. f. Exper. Path. u. Pharm.*, 1924, 1924.
6. Heilmeyer, L.: *Arch. f. Klin. Med.*, 1923, Bd. 171, 1923.
7. Lichtenstein and Lohberg: *Ztschr. f. Klin. Med.*, 1923, 1923.
8. Lichtenstein and Tervet: *Deutsche Arch. of Klin. Med.*, 1923, 1923.
9. Bauer, K.: *Wiener Arch. of Intern. Med.*, 1923, Bd. 23.
10. Kohn: *Arch. f. Klin. Med.*, 1923, 1923.
11. Saks, E. H. and Finkler, B.: *Arch. Med. Mag.*
12. Edman, R. and McMeekin, P. D.: *J. Exper. Med.*, 1923, 1923.
13. Mann, F. G., Sheward, C. H., McMeekin, J. L. and Lister, R. J.: *Am. J. Physiol.*, 74, 1923, 74, 1923, 74, 1923, and 74, 1923.

# Prolongation of Survival Time in Mann-Williamson Dogs by Supplementing Diets With Amino Acids

By

DAVID SHOCH, M.S.

and

SAMUEL J. FOGELSON, M.D.

CHICAGO, ILLINOIS

**I**N the internal duodenal drainage or Exalto-Mann-Williamson dogs the gastro-intestinal tract is altered so that pancreatic and biliary secretions function only in the terminal ileum (Fig. 1.) These dogs usually die in an average of 90 post-operative days from ulceration of the gastrojejunal anastomosis.

In all studies a marked weight loss has been noted. The weight loss or "state of malnutrition" was believed to follow ulceration. This has been reported by Mann (1) and Morton (2.) However, Orndorff, Fauley and Ivy (3) using a bloody stool as an indicator of ulceration and reporting on 42 Mann-Williamson dogs demonstrated that 84 per cent of the weight loss occurred before ulceration. The possible role of weight loss in ulceration has been studied by numerous investigators using varied techniques, such as:

1—Alterations in the level of internal drainage;  
2—Nutritional disturbance without duodenal drainage (4) and 3—Attempts to correlate specific nutritional deficiency with ulcer formation. In this latter field a possible histidine deficiency has been the center of undue attention based upon the scanty experiments of Weiss and Aron (5.) Their work has for practical purposes been refuted by more thorough and better controlled experiments (6, 7), with true statistical evaluation of results. For example, it has been reported that in the Mann-Williamson dogs on so-called histidine therapy survival periods were up to 10 weeks, whereas Orndorff, Fauley and Ivy (3) showed that such dogs on no therapy may survive an average of 12 weeks.

Alteration of the level of duodenal drainage was attempted by various workers. Jenkins and Palmer (8) studied a large series of dogs in which the duodenal drainage level was varied from near the gastrojejunostomy to the cecum. They concluded that dogs with more proximal implantation of the duodenum survived longer.

More recently Slive, Bachrach and Fogelson (9) in attempting to determine the significance of nutrition and gastric acidity in the etiology of experimental peptic ulcer prepared a series of dogs in which the distal end of the duodenum was anastomosed to the small intestine at a point 120 cm. distal to the gastrojejunal anastomosis instead of 40 cm. from the ileocecal valve as is usually done in the Mann-Williamson dog. This increased the area available for pancreatic and biliary action and therefore provided a more adequate nutritive state.

Following this a second operation was performed.

From the Departments of Surgery and Physiological Chemistry,  
Northwestern University Medical School.  
Submitted September 15, 1941.

removing a length of small intestine so that the duodeno-ileal anastomosis was now 40 cm. from the ileocecal valve. In these animals the acidity was unaltered but the survival time decreased, incidence of ulcer increased and weight loss increased markedly. This supports the theory that nutrition plays an important role in the development of experimental ulcers.

An early attempt to evaluate the nutritional aspects of experimental ulcer was made by Fauley and Ivy (10.) They fed Mann-Williamson dogs a standard dog food enriched with raw glandular tissue and liver. Such a supplemented diet increased the survival time of these dogs to 186 days or almost twice the usual survival time.

Our work is a direct outgrowth of the latter experiment. We fed a pre-digested protein supplement sufficient to meet the animals' nitrogen needs. This should elicit a minimum of digestive effort from the gastro-intestinal tract of the Mann-Williamson dog and allow more absorption to take place.

## METHODS

The Mann-Williamson operation was performed on 25 normal dogs. Fifteen of these were placed on the following diet:

### Diet No. 1—Amino acid diet

|                    |                 |                  |
|--------------------|-----------------|------------------|
| Glucose            | 6 gm. kilo/day  | 24 cal. kilo/day |
| Dextri Maltose     | 5               | 20               |
| Powdered Skim Milk | 5               | 20               |
| Amino Acids        | 1               | 4                |
| Whole Milk         | 30 cc. kilo/day | 20               |
| Water              | ad lib          |                  |
|                    |                 | 88               |

N intake from Amino Acid- 0.16 gms. kilo/day  
N intake besides Amino Acids 0.41

Total N intake 0.60

Ten dogs were placed on the following diet:

### Diet No. 2—Casein control diet

|                    |                 |                  |
|--------------------|-----------------|------------------|
| Glucose            | 6 gms. kilo/day | 24 cal. kilo/day |
| Dextri Maltose     | 5               | 20               |
| Powdered Skim Milk | 5               | 20               |
| Casein             | 1               | 4                |
| Whole Milk         | 30 cc. kilo/day | 20               |
| Water              | ad lib          |                  |
|                    |                 | 88               |

N intake from Casein 0.16 gms. kilo/day  
N intake besides Casein 0.44

Total N intake 0.60

The casein used in the control diet was a crude casein.\* The amino acids were various commercial protein digests.† To both diets were added adequate amounts of the Vitamin B complex in the form of Brewer's yeast and all the essential minerals.

As can be seen from the above tables the diets are identical as to content, caloric and nitrogen intake. The one factor differentiating the two diets is the

table the survival times of the dogs in the two series were: Average of 15 dogs on amino acid diet—52 weeks with a range of from 13 to 80 weeks. Average of 10 dogs on casein diet—19 weeks, with a range from 3 to 49 weeks.

In spite of the wide variations in survival time and the overlapping, statistical analysis of the figures indicate a significant difference between the two

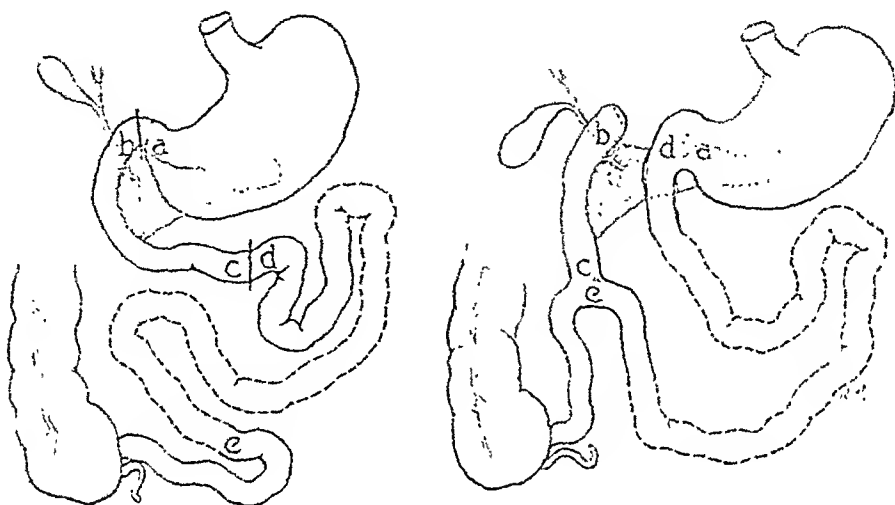


Fig. 1

substitution of amino acids for casein in Diet 1. By thus limiting the number of variables to one, it is possible to correlate any change in survival time, incidence of ulcer and the nutritional state with the differentiating factor, i.e. feeding of amino acids.

The feeding of the above preparations was normally begun on the sixth post-operative day and continued until the death of the animal. During the life of the animals blood studies were made at least semi-monthly and gastric analyses run at least once a month.

### RESULTS

The actual survival times for the dogs used in this experiment are represented in Table I. As seen in this

\*Generously supplied by Mead-Johnson & Company.

†Generously supplied by Mead-Johnson & Company, Baxter Laboratories and Frederick Stearns & Company.

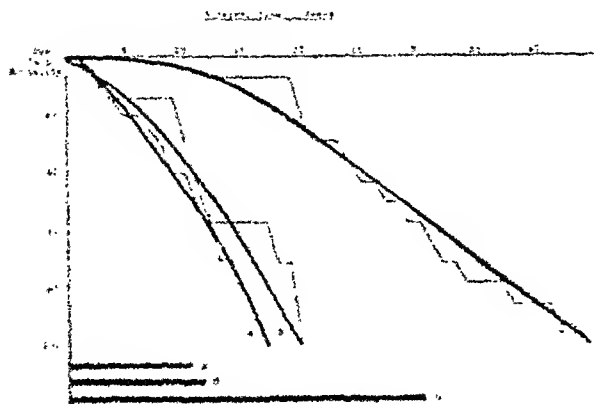


Fig. 2

series. To better illustrate the effect of amino acid feedings, the survival time is plotted against the per cent mortality (Fig. 2.) In order to make the curve as smooth as possible the extremely long survival time of one dog in each series (No. 8 and 18) has been omitted. The horizontal straight lines indicate the average survival time of the two series of dogs in this experiment and a third series of 42 dogs on a stock diet with no medication has been included for comparison (3.)

The dark smooth lines represent a curve averaging the experimental results in each case. As can be seen the dogs on the amino acid diet far outlived those on

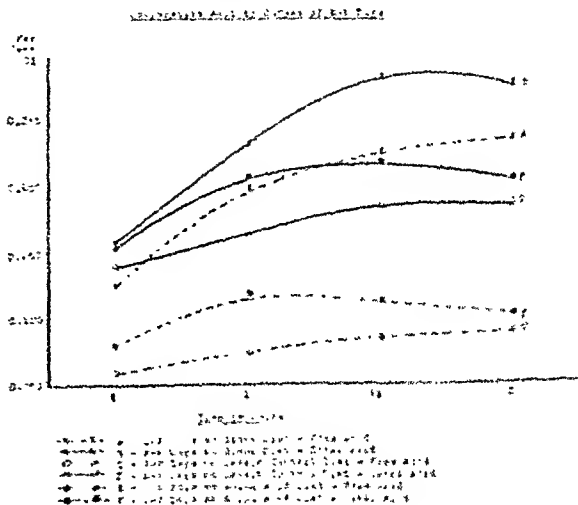


Fig. 3

TABLE I  
*Dogs on protein digest*

| Dog No. | Post-Operative Days of Survival | Incidence of Ulcer | Remarks  |
|---------|---------------------------------|--------------------|--|
| 1       | 236 days                        | 220 days           | Shallow ulcer—death due to lung complications.   |
| 2       | 291                             | 248                | Shallow non-perforating ulcers.  |
| 3       | 139                             | 85                 | Large perforated ulcer.  |
| 4       | 219                             | 109                | Small perforated ulcer.  |
| 5       | 93                              | 74                 | Large perforated ulcer.  |
| 6       | 205                             | 175                | Perforated ulcer.  |
| 7       | 170                             | 123                | Perforated ulcer.  |
| 8       | 358                             | 316                | On 540th day taken off A.A. diet and placed on stock diet. Shallow ulcer found at death. Some blood in stomach and obstruction in bowel. |
| 9       | 146                             | 129                | Perforated ulcer.  |
| 10      | 169                             | 132                | Killed by ether—No ulcer, jejunitis, some hemorrhage.  |
| 11      | 311                             | 293                | Perforated ulcer.  |
| 12      | 269                             | 249                | Perforated ulcer.  |
| 13      | 175                             | 158                | Perforated ulcer.  |
| 14      | 223                             | 200                | Non-perforated ulcer.  |
| 15      | 112                             | 120                | No ulcer. Some hemorrhage into stomach.  |

Average 223 days or 32 weeks.

*Control dogs on casein diet*

|    |          |          |  |
|----|----------|----------|--|
| 16 | 145 days | 123 days | Large perforated ulcer.                          |
| 17 | 24       | 22       | Large perforated ulcer.                          |
| 18 | 340      | —        | No ulcer—terminal ileitis and nodular pneumonia. |
| 19 | 142      | —        | No ulcer.  |
| 20 | 123      | 100      | Perforated ulcer.                                |
| 21 | 86       | 64       | Perforated ulcer.                                |
| 22 | 74       | 41       | Perforated ulcer.                                |
| 23 | 67       | 46       | Perforated ulcer.                                |
| 24 | 67       | 43       | Shallow ulcer—hemorrhage                         |
| 25 | 246      | 216      | Perforated ulcer.                                |

Average 131 days or 19 weeks.

the stock diet or on the casein diet. This is very significant because up to very recently no one has been able to keep Mann-Williamson dogs alive more than 90 days. In the last year work has been published showing the efficacy of aluminum phosphate (11) and Enterogastrone (12) in preventing experimental ulcer, but on a straight nutritional basis our figures for longevity of Mann-Williamson dogs are still unsurpassed.

As mentioned before blood and gastric studies were performed throughout the post-operative life of the dogs. The blood determinations included red and white cell counts, total proteins, albumin, globulin (by difference) and N.P.N. These values varied from week to week, but remained fairly constant until the development of the ulcer when the total protein and the albumin/globulin ratio fell and the animals became severely anemic from loss of blood (Table II.)

Fractional gastric analyses were made over a two hour period in response to 7 per cent alcohol and secretory curves are given below (Fig. 3.) Here again the curves are compared with those of a series of Mann-Williamson dogs on a stock diet. As can be seen on the graph there is relatively little difference in the two curves either in height or duration.

An important part of the observations on the dogs in this experiment was the recording of weights at regular intervals. These were made in an attempt to note whether the amino acid preparations would maintain the weight of the dogs. In Table III the pre-operative weights are recorded together with weight when diet was begun (5-6 days post-operatively), weight at incidence of ulcer (as indicated by blood in stool) and weight at death. These are expressed as per cent of pre-operative weight. Per cent weight loss immediately after operation is about the same for the two series (87 and 82 per cent.) Weight at death shows a little larger deviation, but the only significant difference occurs at the incidence of ulcer where dogs on the amino acid diet have lost an average of only 20 per cent of the pre-operative weight, while the dogs

TABLE II  
*Blood picture in typical dog in series*  
Dog No. 2

| P.O. Day | Red Cells | White Cells | Gm. Hb. 100 cc. | Gm. Total Protein 100 cc. | Gm. Albumin 100 cc. | Gm. Globulin 100 cc. | Mgms. N.P.N. 100 cc. |
|----------|-----------|-------------|-----------------|---------------------------|---------------------|----------------------|----------------------|
| 76       | 4.5       | 11.2        | 14.5            |                           | 4.46                |                      | 37.4                 |
| 83       | 4.4       | 15.5        | 15.0            | 7.81                      | 4.68                | 3.13                 | 10.0                 |
| 96       | 6.2       | 10.0        | 14.3            | 7.33                      | 5.99                | 3.34                 | 33.7                 |
| 103      | 6.3       | 16.0        | 14.3            | 7.62                      | 5.80                | 1.82                 | 33.3                 |
| 126      | 7.0       | 20.0        | 15.0            | 7.51                      | 4.78                | 3.03                 | 34.6                 |
| 138      | 6.7       | 15.0        | 15.0            | 7.44                      | 2.87                | 3.54                 | 36.1                 |
| 152      | 6.3       | 17.2        | 14.5            | 7.33                      | 4.72                | 2.61                 | 31.4                 |
| 175      | 7.4       | 13.0        | 14.0            | 8.13                      | 5.00                | 3.13                 | 38.9                 |
| 209      | 5.1       | 10.9        | 13.5            | 7.10                      | 3.61                | 3.49                 | 39.3                 |
| 245      | 4.9       | 20.4        | 12.0            | 6.05                      | 4.11                | 1.92                 | 33.5                 |
| 257      | 4.2       | 23.0        | 7.5             | 6.7                       | 3.67                | 3.03                 | 37.3                 |
| 278      | 3.4       | 15.8        | 6.0             | 5.5                       | 3.05                | 2.40                 | 24.15                |
| 286      | 2.5       | 7.0         | 4.0             | 6.0                       | 4.03                | 2.00                 | 45.55                |

291—Found dead—shallow ulcer.

TABLE III  
Weights of fifteen dogs on amino acid diets

| Dog No. | Pre-Operative Weight | Immediate Post-Operative Weight | Per Cent of Pre-Operative Weight | Weight at Incidence of Ulcer | Per Cent of Pre-Operative Weight | Weight at Death | Per Cent of Pre-Operative Weight |
|---------|----------------------|---------------------------------|----------------------------------|------------------------------|----------------------------------|-----------------|----------------------------------|
| 1       | 27 lbs.              | 22 lbs.                         | 81%                              | 23 lbs.                      | 85%                              | 15 lbs.         | 55%                              |
| 2       | 33                   | 31                              | 94                               | 34                           | 103                              | 29              | 88                               |
| 3       | 51                   | 43                              | 84                               | 32                           | 63                               | 24              | 47                               |
| 4       | 41                   | 35                              | 85                               | 37                           | 91                               | 25              | 61                               |
| 5       | 32                   | 30                              | 94                               | 27                           | 84                               | 23              | 72                               |
| 6       | 17                   | 16                              | 94                               | 16                           | 94                               | 12              | 71                               |
| 7       | 39                   | 27                              | 69                               | 25                           | 64                               | 17              | 43                               |
| 8       | 26                   | 23                              | 89                               | 26                           | 100                              | 23              | 88                               |
| 9       | 24                   | 24                              | 96                               | 19                           | 79                               | 17              | 71                               |
| 10      | 26                   | 21                              | 81                               | 17                           | 65                               | 17              | 65                               |
| 11      | 35                   | 30                              | 86                               | 26                           | 74                               | 25              | 72                               |
| 12      | 23                   | 17                              | 74                               | 16                           | 70                               | 12              | 52                               |
| 13      | 34                   | 27                              | 79                               | 22                           | 65                               | 20              | 59                               |
| 14      | 15                   | 13                              | 87                               | 11                           | 73                               | 9               | 60                               |
| 15      | 22                   | 19                              | 86                               | 17                           | 77                               | 15              | 68                               |
| Average |                      |                                 | 87%                              |                              | 80%                              |                 | 64%                              |

Weights of ten dogs on casein diet

| Dog No. | Pre-Operative Weight | Immediate Post-Operative Weight | Per Cent of Pre-Operative Weight | Weight at Incidence of Ulcer | Per Cent of Pre-Operative Weight | Weight at Death | Per Cent of Pre-Operative Weight |
|---------|----------------------|---------------------------------|----------------------------------|------------------------------|----------------------------------|-----------------|----------------------------------|
| 16      | 32 lbs.              | 28 lbs.                         | 87%                              | 19 lbs.                      | 59%                              | 17 lbs.         | 53%                              |
| 17      | 25                   | 17                              | 68                               | 15                           | 60                               | 14              | 56                               |
| 18      | 28                   | 22                              | 81                               | —                            | —                                | 11              | 39                               |
| 19      | 24                   | 22                              | 92                               | —                            | —                                | 14              | 58                               |
| 20      | 29                   | 15                              | 52                               | 11                           | 38                               | 10              | 34                               |
| 21      | 21                   | 17                              | 81                               | 11                           | 52                               | 8               | 38                               |
| 22      | 23                   | 21                              | 91                               | 16                           | 70                               | 16              | 70                               |
| 23      | 25                   | 20                              | 80                               | 17                           | 68                               | 13              | 52                               |
| 24      | 19                   | 16                              | 84                               | 14                           | 74                               | 10              | 53                               |
| 25      | 21                   | 19                              | 90                               | 16                           | 76                               | 14              | 67                               |
| Average |                      |                                 | 82.3%                            |                              | 63%                              |                 | 54%                              |

on the casein diet have lost 47 per cent of their original weight.

### CONCLUSIONS

1. By feeding a supplement of pre-digested protein to Mann-Williamson dogs we were able to prolong the survival time and delay the appearance of ulcer.
2. We were not able to prevent the ulcers from forming.

3. Blood studies were negative and gastric analyses showed no difference from analyses run on Mann-Williamson dogs on a stock diet.

4. Our success in materially delaying the appearance of ulcer and prolonging the life of Mann-Williamson dogs indicates the importance of an easily digestible and absorbable diet in the etiology of the experimental ulcer.

### REFERENCES

1. Mann, F. C.: The Chemical and Mechanical Factors in Experimentally Produced Peptic Ulcer. *S. Clin. N. Amer.*, 5:753, 1925.
2. Mann, F. C.: Observations on Peptic Ulcer. *Ann. Surg.*, 77:191, 1923.
3. Orrick, J. R., Fauley, G. B. and Ivy, A. C.: Prophylactic Value of Gastric Mucin in the Therapy of Post-Operative Jejunal Ulcer. *Am. J. Dig. Dis.*, 8:28, 1933.
4. McMaster, P. L.: Experimental Spontaneous Peptic Ulcer. *Proc. Soc. Exp. Biol. Med.*, 29:282, 1932-33.
5. Weiss, A. G. and Aron, E.: Role of Amino Acids in the Genesis of Experimental Ulcer. Effect of Histidine. *Proteins*, 4:185, 1937.
6. Sanderson, D. J., Seligson, H. C. and Glazer, W. S.: The Value of Histidine in Prevention of Experimental Ulcer in Dogs. *Am. J. Dig. Dis.*, 1:28, 1937.
7. Wu, P. P.: The Effect of Histidine on the Experimental Production of Peptic Ulcer. *Am. Surg.*, 15:100, 1927.
8. Jenkins, H. P. and Palmer, W. L.: Studies on Experimental Jejunal Ulcer. *Proc. Soc. Exp. Biol. and Med.*, 7:214, 1937-38.
9. Shier, A., Backus, W. and Ferguson, R. J.: The Significance of Nutrition and Gastric Activity in the Etiology of Experimental Peptic Ulcer. *S. G. O.*, 70:725, 1929.
10. Fauley, G. B. and Ivy, A. C.: The Prevention of Post-Operative Ulcers by Diet and Purgation. *S. G. O.*, 63:77, 1926.
11. Fauley, G. B., Freeman, E., Ivy, A. C., Atkinson, A. J. and Winsted, R. S.: Aluminum Phosphate in the Therapy of Peptic Ulcer. *Arch. Int. Med.*, 67:263, 1941.
12. Hardy, A. P., Fauley, G. B., Greenwald, H., Preston, F. W. and Ivy, A. C.: Prevention of Experimental Gastrojejunal Ulcer by Enteroculture. *Am. J. Physiol.*, 123:214, 1943.

# Acute and Chronic Cecal Volvulus\*

By

DONOVAN C. BROWNE, M.D.

and

GORDON McHARDY, M.D.

NEW ORLEANS, LOUISIANA

**I**N foreign publications, predominantly from Russia, Finland, Poland and Scandinavia, cecal volvulus is a relatively frequent precipitant of acute intestinal obstruction; Jacobsen gave it an 11.6 percentage. In American literature it is of unusual occurrence; Sweet's statistical study shows a 1.15 percentage.

With few exceptions acute cecal volvulus has been reported. There is, however, adequate basis for diagnosing a chronic type; certain degrees of torsion permitting spontaneous rectification.

Pathological embryologic development resulting in lack of fixation of the cecocolon renders possible a variety of cecal displacements. Cecums that could rotate were found in 24.1 per cent of cadavers (combined statistics of Treves, Smith, Thim and Wandel.) Obviously such pathological anatomy rarely causes trouble.

## CLASSIFICATION

The common classification is—clockwise torsion and anti-clockwise torsion—the former being the more common variety.

Graham classifies three types by position: (1) Cecal bascule, the posterior cecal surface looks forward, axis of rotation is transverse; (2) rotation in an oblique axis, the cecum occupying the umbilical or left hypochondriac region; (3) rotation of the cecum about its long axis.

More important than the direction of twist and the position the caput cecum points at the end of its pathological wandering is the degree of torsion. This has varied greatly in published case reports. Many a half turn of the cecum upon itself (180 degrees) has been described as one complete turn (360 degrees.) A half twist is sufficient to produce complete obstruction, further torsion adds vascular strangulation.

## PATHOLOGIC CHANGES

When the cecum undergoes rotation around its mesenteric axis an isolated loop is formed and the vessels supplying the region are torsed. Increased distension impairs the blood supply by capillary compression. Increased permeability of the intestinal wall with anoxemia, necrosis and gangrene are inevitable unless there is early surgical intervention.

## SYMPTOMS

There is no distinctive clinical picture. No age group is exempt. Sexual incidence is not helpful, but developmental variation is more common to the female. Acute intestinal obstruction develops with startling rapidity. The colicky pain is progressive and may localize in the right mid-abdomen supposedly at the

site of torsion. Tenderness is expected to be more acute over the cecum. Distension is marked, no cecal prominence is recorded. Ohman suggested measurement of bowel capacity to localize the site.

Chronically recurring volvulus results in obstructive manifestations of variable severity with colicky right abdominal pain.

## DIAGNOSIS

In the acute intestinal obstruction due to cecal volvulus the cause is rarely determined prior to exploratory or necropsy.

When compatible symptoms accompany a roentgenologically demonstrable mobile cecum the possibility of a chronic cecal volvulus may be considered. Proof depends upon a symptomatic response to cecopexy. It is not unlikely that removal of a chronic appendix may produce cecal fixation thereby giving symptomatic relief of a chronic cecal volvulus.

## PROGNOSIS

In acute obstructive cecal volvulus without surgical intervention the patient dies. This is exemplified in Chalfant's review.

The mortality with the different surgical procedures depends upon: (1) the time interval which has elapsed and the degree of mechanical and vascular interference; (2) the surgical ability of the operator.

## TREATMENT

The correction of cecal volvulus is an emergency operative procedure. If diagnosable the surgical management of the chronic variety is elective. In addition to surgery every case calls for supportive measures to combat the effects of acute intestinal obstruction.

In general the simplest measure to relieve the obstruction, decompress the distended cecum, release the vascular interference and prevent recurrence must be decided at the time. For the explored patient one of four procedures is considered, the choice depending on the general condition of the patient, the type of defective development, the extent of cecal damage, the status of the mesenteric vessels and, of course, the surgeon's skill.

(1) Rectifying torsion by simply untwisting the volvulus is acceptable when the patient's condition contra-indicates further surgery. Where omental, inflammatory or congenital bands contribute to the pathology these should be eliminated.

(2) Cecoplication to the tendon of the psoas minor muscle, to the anterior abdominal wall or to the parietal peritoneum of the cecal fossa offers a cecopexy which may be resorted to when cecostomy is not considered essential to decompression of the bowel.

\*From the Department of Medicine, Tulane University School of Medicine, and the Gastro-Enterologic Clinic of Toussaint Infirmary, New Orleans, La.  
Submitted August 8, 1941.



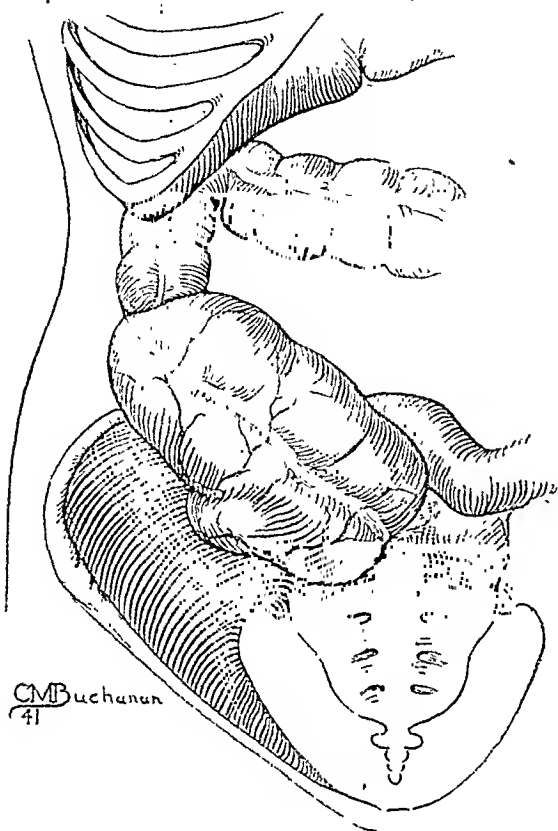


Fig. 1

(3) Radical resection is reserved for those cases in which the viability of the segment is questioned. Resection with primary ileotransversecolostomy is the method of choice; exteriorization and double barrel colostomy is occasionally indicated with restitution of the tract to be effected if the patient survives. Extirpation of a gangrenous cecum in cases of cecal volvulus carries a 50 per cent mortality.

(4) Cecostomy of the untwisted, cecum, anatomical placement and bringing the Pezzar catheter out through a stab wound in the right iliac region will by the resultant inevitable peritoneal reaction result in fixation of the cecum to the corresponding parietal peritoneum, accomplishing a "cecopexy." Cecostomy actively reducing the distension simplifies anatomical orientation. The mortality approximates 17 per cent.

Detorsion and cecopexy by cecostomy offers the best prognosis. Mere untwisting of the volvulus is not satisfactory in that recurrence is likely. Cecopexy by other methods is not superior and is only practical in chronic volvulus. The mortality of resection with or without exteriorization limits the use of this procedure to cases hopeless if managed otherwise.

#### CASE REPORTS

The following six proven instances of cecal volvulus add considerably to the reported cases of the American literature. Our statistical study at Touro Infirmary covering 1924 through 1940 shows 172,158 admissions with 411 instances of acute intestinal obstruction of which 6 were proven due to cecal volvulus representing .003 per cent of admissions and 1.4 per cent of obstructions.

Case O-2581. A 27 year old school mistress admitted to the Infirmary on April 3, 1937, with an actively bleeding chronic duodenal ulcer. During the night April 5 she woke with severe persistent stabbing pain in the right upper abdomen, began to vomit and developed severe abdominal distension.

Examination revealed an anemic woman in moderately severe shock. The tympanitic abdomen was symmetrically distended. Tenderness was acute in the right upper quadrant. Roentgen study failed to reveal free peritoneal air. There was fever and a relative neutrophilia.

A pre-operative diagnosis of perforated duodenal ulcer was made.

Exploratory laparotomy six hours subsequent to the onset revealed a markedly dilated cecum twisted upon itself once in a medial direction. The mobile cecum had a long free mesentery; there was no attachment of the ascending colon at the hepatic flexure. The volvulus was rectified. Cecostomy (Pezzar catheter) was performed.

The patient had an uneventful convalescence and four years subsequent to the incident is free of symptomatology referable to her cecum.

Case M-7188. A 28 year old clerk admitted to the Infirmary on October 17, 1935, with an incarcerated right indirect inguinal hernia. Under spinal anesthesia an inguinal hernioplasty was done returning the viable contents of the sac, (ileum, cecum and omentum) into the peritoneal cavity.

The post-operative course was uneventful for 72 hours, then obstructive manifestations recurred with severe sharp pain in the right upper abdomen. The abdomen became markedly and symmetrically distended. Operative intervention was not elected; the patient became progressively worse and expired 48 hours later.

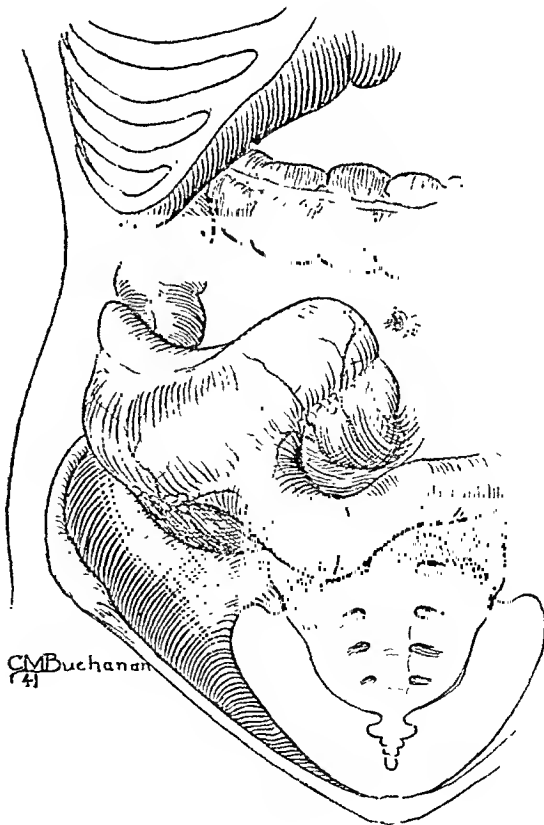


Fig. 2

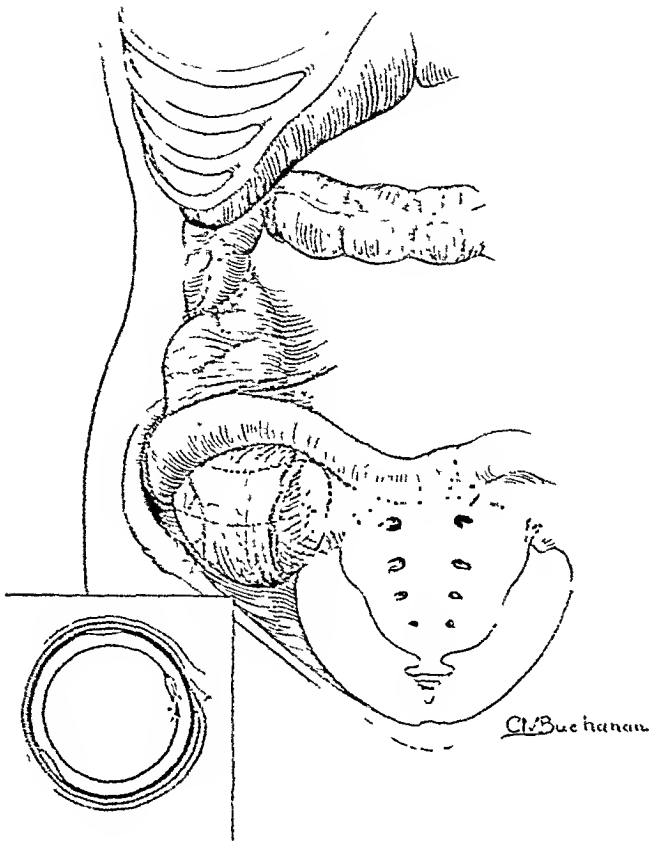


Fig. 3

Necropsy revealed an abnormally mobile redundant cecum with a long mesentery continuous with that of the ileum: fixation was close at the hepatic flexure. The cecum was twisted on itself once, turning medially with the caput occupying the umbilical region, resulting in complete obstruction; there were gangrenous changes in the cecum and terminal ileum. It was apparent that a sliding hernia was properly repaired and that volvulus developed in the unusually mobile cecum.

Case 108-4523. A 16 year old male student admitted to the Infirmary January 2, 1928, with acute appendiceal symptoms. Through a right rectus incision an acute gangrenous appendix was removed without difficulty.

On the seventh post-operative day he suddenly developed severe pain in the right mid-abdomen with associated tenderness, emesis and progressive distension. There was a rapid febrile rise with a leukocytosis of 17,000. Duodenal suction and flushes failed to give any relief.

Exploratory laparotomy on January 9, 1928, revealed cecal volvulus with a complete half turned medially causing complete obstruction of a loop of kinked ileum bound by fresh adhesions. A cecostomy, using a Pezzar catheter relieved the obstruction and the patient had an uneventful convalescence.

A follow-up report twelve years subsequent finds him asymptomatic.

Case 105A-173. A 23 year old physician admitted to the Infirmary because of intractable pain from duodenal ulcer. On June 2, 1927, a posterior gastro-enterostomy and appendectomy were done.

On June 11, when otherwise asymptomatic, the patient developed acute pain localized in the right upper abdomen, followed shortly by vomiting which soon became stercoraceous, the abdomen became markedly distended and there was a sharp febrile rise. There was no palpable mass.

Within six hours after the onset an exploratory laparotomy was done revealing the cecum twisted laterally upon

itself "and attempting to herniate through the ileocecal fosa." (Urban Maes) The abnormally long mesentery was dragged over the "face" of the cecum. After detorsion a cecostomy was done. The cecum was then placed in the right iliac region and held in place by the cecostomy tube. Convalescence was uneventful.

The patient remained free of colonic symptoms. Recurrent ulcer manifestations seven years later indicated a gastric resection from which he did not recover. Autopsy revealed the cecum adherent to the parietal peritoneum of the right iliac fossa in normal anatomical position.

Case P-8764. A 55 year old housewife with no previous gastro-intestinal history admitted to the Infirmary on October 4, 1938, with acute right lower abdominal pain of 24 hours duration. The pain was at first intermittent then constant and of increasing severity. From the onset there was vomiting. Since prior to the onset she was markedly constipated, she took an enema with good results, but accentuation of urgency to stool and tenesmus.

Examination revealed symmetrical abdominal distension without localization or rigidity but with marked tenderness in the right lower quadrant. No mass could be felt. There was a sharp febrile rise and leukocytosis.

Exploratory laparotomy revealed a distended cecum occupying its normal position but twisted upon itself medially one-half turn so that the ileocecal valve was lateral to the torsed cecum. The cecal mesentery was continuous with that of the ileum. After untwisting the volvulus the cecum was in normal position and a cecostomy was performed relieving the distension immediately.

This patient recovered from the surgery uneventfully but eighteen months subsequent, developed symptoms of partial low intestinal obstruction. A barium enema revealed a neoplastic infiltration of the mid-transverse colon.

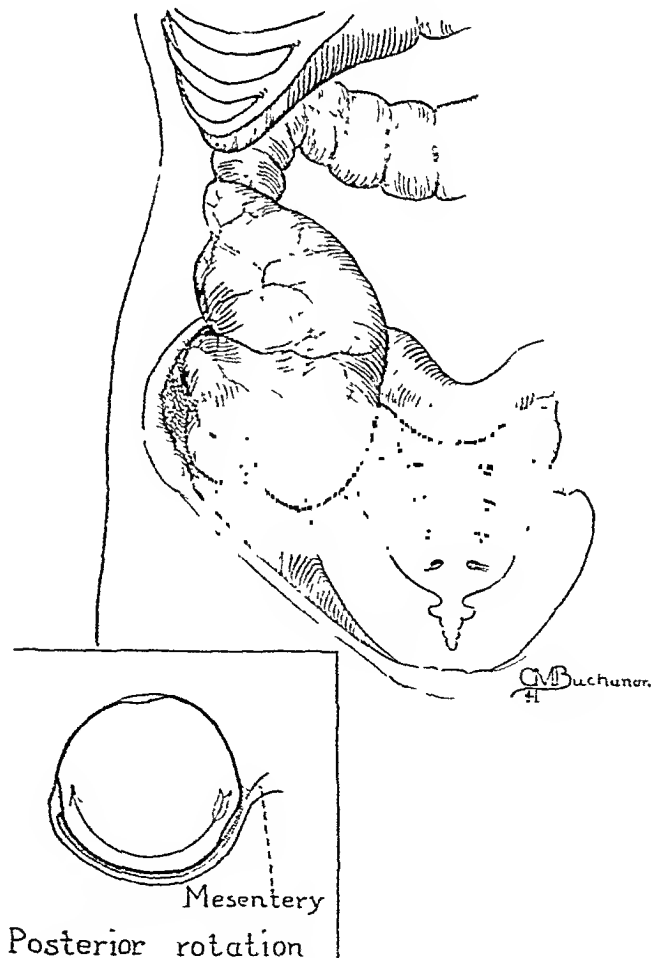


Fig. 4

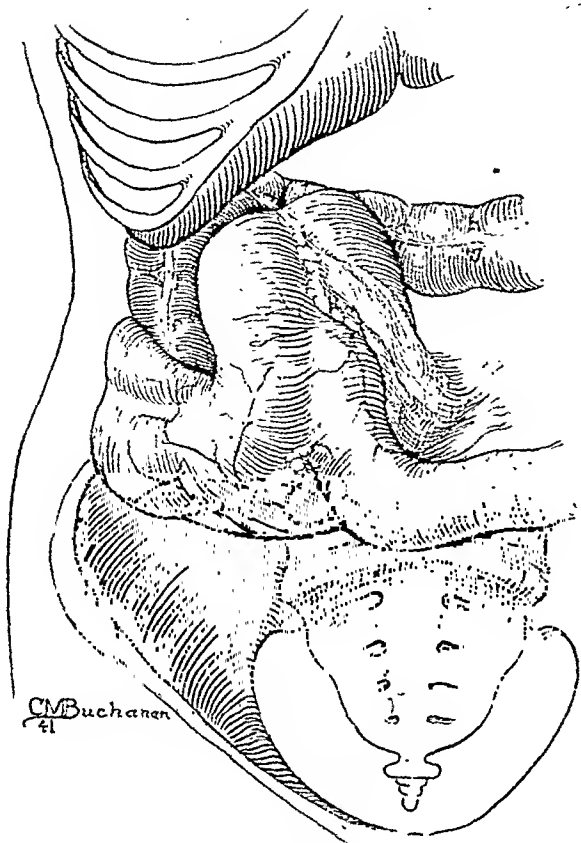


Fig. 5

"The cecum is roentgenologically in normal anatomical position and is well fixed as determined by fluoroscopic manipulation."

Case P-1503. A 40 year old housewife with a history of severe constipation and addiction to laxatives and colonic irrigations. She had experienced intermittent right lower abdominal pain and two episodes suggestive of intestinal obstruction within 18 months which had responded to conservative measures. On February 21 she was admitted to the Infirmary after experiencing progressively severe right upper abdominal pain for 36 hours. There was emesis and progressive distension. Repeated enemas with fair results gave no relief of pain.

Examination revealed an acutely ill, febrile woman with

a markedly distended abdomen with a questionable palpable mass in the right upper quadrant.

X-ray confirmed the low intestinal obstruction.

Exploratory laparotomy revealed a tremendously distended cecum twisted and then bent on itself so that the caput cecum was directly beneath the liver. Rectifying the twist, securing anatomical correction and cecostomy revealed viability of the bowel and permitted passage of fluid and gas through the cecostomy tube as well as into the distal colon. The post-operative was complicated by massive pulmonary collapse upon which was superimposed a pneumonitis from which the patient expired on February 27, 1941. During the six post-operative days the patient had a return of normal gastro-intestinal function apparently indicating proper surgical correction. Autopsy was not permitted.

## DISCUSSION

Acute intestinal obstruction due to cecal volvulus is infrequent for few such instances escape confirmatory surgery or autopsy. A mobile cecum probably can exist without manifesting itself clinically since such abnormal anatomy exists in excess of 24 per cent, but it is likely that many an unexplained abdominal complaint is due to an unrecognized chronic cecal volvulus. Perhaps the therapeutic response to the removal of many a chronic appendix may be due to the resultant cecal fixation.

Since surgical management alone is of therapeutic value and, regardless of the elected procedure, the mortality in the acute obstructive cases is startlingly high, it seems practical to advise cecopexy if a diagnosis of subacute or chronic cecal volvulus is made.

## CONCLUSIONS

1. We herewith add six illustrative case reports of acute intestinal obstruction due to cecal volvulus to the limited literature on the subject. Three of our cases were post-operative equaling the total published instances encountered in our review of the literature. Our statistical study reveals an incidence of only 1.4 per cent among 411 cases of acute intestinal obstruction.

2. A clinical diagnosis of acute cecal volvulus is seldom made since there are no diagnostic criteria that render a clinical diagnosis feasible. However, cecal volvulus must be considered in making a diagnosis in obscure cases of intestinal obstruction.

3. Chronic cecal volvulus is an entity rarely encountered and probably overlooked in many instances of unexplained abdominal pain.

## BIBLIOGRAPHY

- Basden, M. M.: Volvulus of Cecum Complicating Labor. *Brit. Med. J.*, 1:1119, 1934.
- Bekker, E. K. S.: Acute Obstruction Caused by Volvulus of Cecum. *Pract. Med.*, 21:663-666, 1939.
- Biechelor: True Volvulus and Gangrene of Cecum. *Tunisia Med.*, 33:371-373, 1939.
- Chalfant, S. A.: Torsion of the Cecum with Review of the Literature. *Am. J. Obst. and Gynec.*, 2:597-600, 1921.
- Corner, E. M. and Sargent, W. P. G.: Volvulus of the Cecum. *Ann. Surg.*, 41:63, 1905.
- Counseller, V. S.: Discussion of Pratt and Fallis' article. *J. A. M. A.*, 89:1225, 1927.
- Desjardins: Cecal Volvulus; Roentgen Diagnosis. *Lyon Chir.*, 36:445-447, 1939.
- Dixon, C. F. and Miller, J. M.: Volvulus of the Cecum, a Post-Operative Complication. *Minn. Med.*, 23:250-251, 1940.
- Gatellier, J., Moutier, F. and Porcher, P.: Les volvulus due coecum. *Arch. d. mal de l'app. digestif.*, 21:20, 1931.
- Grace, A. J.: Volvulus of Cecum. *Canad. M. A. J.*, 38:346-351, 1938.
- Gusynin, V. A.: Clinical Basis Resection of Cecum in Case of Volvulus. *Vestnik. Khir.*, 56:465-471, 1938.
- Harvey, S. C.: Congenital Variations in the Peritoneal Relations of the Ascending Colon, Cecum, Appendix and Terminal Ileum. *Ann. Surg.*, 67:641-656, 1918.
- Hulman, C. C.: Cecal Volvulus Assoc. with Reversed Rotation of Middle Gut. *Lancet*, 2:101-102, 1940.
- Homan, J.: Torsion of the Cecum and Ascending Colon. *Arch. Surg.*, 3:395, 1921.
- Jacobson, J.: Volvulus Due Caecum. *Acta Chir. Scandiae.*, 56:181, 1923.
- Labry, R. and Godinot, C.: Cecal Volvulus with Ileocecal Invagination. *Lyon Med.*, 163:326-329, 1939.
- Miller, J. M. and Clagett, O. T.: Volvulus of Ileocecocolic Region. *Proc. Staff Meet. Mayo Clinic*, 15:424, 1940.
- McGowan, J. M. and Dixon, C. F.: Volvulus of the Cecum. *Proc. Staff Meet. Mayo Clinic*, 11:337, 1936.
- Mukhina, M. V.: Cecal Volvulus. *Vestnik Khir.*, 56:455-464, 1938.
- Nelson, J. M.: Post-Operative Volvulus of Cecum. *Am. J. Surg.*, 5:398, 1928.
- Pratt, J. P. and Fallis, L. S.: Volvulus of the Cecum and Ascending Colon. *J. A. M. A.*, 89:1225-1229, 1927.
- Rokitsky, C.: Intestinal Strangulation (8 cases). *Arch. Gen. Med.*, 14:202, 1937.
- Smith, G. M.: A Statistical Review of the Variations in the Anatomic Positions of the Cecum, etc. *Anat. Rec.*, 5:549-557, 1911.
- Sweet, R. H.: Volvulus of Cecum. *New Eng. J. Med.*, 213:287, 1935.
- Treyes, F.: Lectures on Anatomy of the Intestinal Canal, etc. *Brit. M. J.*, 1:415-419-470-474-527-530-550-553, 1885.
- Udarnok, E.: Volvulus of the Cecum Mobile. *Rev. San. Med. Bucuresti*, 37:157-159, 1938.
- Vasiliu, I. and M.: Intestinal Occlusion Due to Volvulus of Cecum. *Rev. San. Med. Bucuresti*, 36:165-169, 1937.
- Verardo, A.: Acute Volvulus of Cecum. *Boll. e mem. Soc. primontese di chir.*, 9:559-564, 1939.
- Weble, R. E.: Volvulus. *S. G. O.*, 19:644, 1914.
- Weinstein, M.: Volvulus of Cecum and Ascending Colon. *Ann. Surg.*, 107:248-259, 1938.

# Indeterminate Fever Caused by Perirectal Abscess

By

WILSON WEISEL, M.D.,\* E. G. WAKEFIELD, M.D.†

and

NEWTON D. SMITH, M.D.‡

ROCHESTER, MINNESOTA

**W**E have thought it worth while to call attention to the fact that in cases of fever for which no cause can be found, the physician should consider the possibility of a perirectal abscess.

## METHOD

Records of those 912 patients for whom the diagnosis of "perirectal abscess" had been made at the Mayo Clinic during the years from 1930 to 1939 were called from the files, together with the records of those 630 patients for whom the diagnosis of "indeterminate fever" had been made during the same period. We next selected records of those patients who at some time during their illness had presented the problem of clinically significant fever for which for awhile no cause could be found, but which eventually was found to have been caused by perirectal abscess. We have excluded all cases in which a coexisting disease might have been held accountable for the fever. We have further excluded all cases of chronic ulcerative colitis, regional enteritis, carcinoma of the terminal part of the colon, diverticulitis and also cases in which patients had recently undergone perineal or rectal surgical procedures.

## DIAGNOSTIC CONSIDERATIONS

*Pathogenesis of perirectal abscess.* It has been pointed out elsewhere (1) that the presence of a perirectal abscess often causes confusion in the diagnosis of pathologic processes involving the terminal portion of the colon and anal canal, and this confusion may well extend to the clinical manifestations of such processes, such as fever. The pathogenesis of perirectal abscess has been clearly described by Buie (2), who had divided it into three stages. The first stage is that of infection in, or injury to, the crypts of Morgagni or the anorectal region; the second stage is that of extension of the infection, which may take place in various directions; the third stage is that of formation of abscess, and the abscess may finally rupture spontaneously or be drained surgically.

*Symptomatology aspects.* In the first group (912 cases in which the diagnosis of perirectal abscess had been made) we found eleven patients who had presented obscure fever before a correct diagnosis was reached. This was an incidence of approximately one in eighty-three cases for this particular group. In the second group (630 cases in which the diagnosis of indeterminate fever had been made) we found none in which, by means of records and follow-up methods at our disposal, the fever could be ascribed to perirectal abscess. The incidence of fever of indeterminate

origin, therefore, for the entire series of 1,542 cases was one in 142 cases.

In Table I the eleven cases of perirectal abscess in which a preceding period of puzzling fever was present are summarized briefly. It will be noted that these eleven cases have been subdivided into three different classifications: (1) those in which the patients presented obscure fever before and after their admission to the clinic, (2) those in which the patients gave a history of indeterminate fever but in which the correct diagnosis had been made or suspected on the patients' admission, and (3) those in which perirectal abscess had complicated the convalescence of patients by causing an elevation of temperature which was not due to the primary pathologic process under consideration.

## REPORT OF A CASE

In addition to the cases previously summarized, we should like to present an additional and separate case which we believe illustrates well the problems encountered when patients who have obscure fever caused by perirectal abscess are confronted. This case was not included in our series, however, because the patient came to the clinic previous to 1930.

A white, forty-seven year old man presented himself at the clinic complaining of exhaustion and fatigue. His personal, family and marital histories were irrelevant, and a review of the symptoms in his illness did not help. He had lost about 14 pounds (6.4 kg.) during the week preceding his entry to the clinic. Physical examination revealed a temperature of 102° F. (38.8° C.), but there were no other significant observations. The patient was hospitalized for observation.

During hospitalization, laboratory procedures were performed repeatedly for the patient, including examination of smears of sputum, culture of blood and sputum, examination and culture of stools, blood agglutination tests for typhoid fever, paratyphoid fever and undulant fever, a Wassermann test and making of roentgenograms of the thorax, teeth and sinuses, results of all of which were reported as negative. Results of studies of the blood were consistently normal. Leukocytes varied from 4,800 to 8,400 per cubic millimeter of blood, except for one determination out of ten, in which the number reached 11,600. Examination of blood smears disclosed nothing of diagnostic importance and differential counts revealed a ratio of approximately 60 polymorphonuclear leukocytes to 40 lymphocytes. The absence of malarial parasites also was noted repeatedly. Urinalyses showed occasional albuminuria of grade 1 or grade 2, but consistently negative results of examination of sediment were obtained and a normal specific gravity was found.

The patient's course in the hospital was discouraging. He lost strength and weight, and his temperature was of the "swinging," septic type. It varied from 97° to 103° F. (36.1° to 39.4° C.) There were no further definite or localizing symptoms.

Results of repeated physical examinations were nega-

\*Fellow in Surgery, Mayo Foundation.

†Division of Medicine.

‡Section on Proctology, Mayo Clinic.

Submitted January 13, 1942.

live until the fortieth hospital day, at which time a region of marked induration and tenderness was found in the right wall of the rectum. Perirectal abscess was suspected. It was treated by the application of hot packs and it ruptured spontaneously. A large quantity of foul, purulent material drained from it. A huge abscess cavity subsequently was felt in the right ischio-ano-rectal region. Subsequent to the rupture of the abscess the patient's temperature decreased to normal, and remained at normal. The patient began to regain normal strength and weight. He was dismissed after a total of three and a half months of observation. At dismissal his temperature was normal. Subsequent examinations revealed him to be healthy, with a scarred but competent anus.

### COMMENT

In the series of cases we have mentioned, no definite correlation was evident among such factors as age, sex, symptoms, signs, duration of symptoms, or clinical course. Ages varied from twenty-two to sixty-seven years, and distribution according to sex in the group of eleven cases concerned herein was six males to five females. The duration of periods of elevated temperature ranged from five days to one year. In general, we were impressed by the fact that involvement of perirectal tissue in this series of cases was

considerably more extensive than is usually seen in the average instance of perirectal abscess.

In contrast to the characteristic clinical picture of abscess, the usually severe local symptoms and signs were lacking. The occurrence of urinary symptoms in five of the eleven patients (four men and one woman) was interesting, and actually the urinary distress was the principal complaint of these patients.

It may be the variegated character of the condition and course of these patients that made clinical interpretation confusing, and it is especially to be noted that the correct diagnosis in each case was suspected or confirmed only after repeated, physical, and particularly rectal, examination.

On the basis of study of twelve cases of indeterminate pyrexia in which the condition was proved to have been caused by perirectal abscess, we conclude that the condition of perirectal abscess should be kept in the physician's mind in the differential diagnosis of hyperpyrexia of obscure origin.

### REFERENCES

1. Smith, N. D.: Anal Abscess and Anal Fistula. *J. Oklahoma M. A.*, 27:219-232, July, 1934.
2. Baile, L. A.: *Practical Proctology*. Philadelphia, W. B. Saunders Company, pp. 127-137, 1935.

TABLE I

*Indeterminate fever caused by perirectal abscess: symptoms, observations, treatment in eleven cases*

| Case  | Age, Sex | Temperature (F.), Duration          | Symptoms                                | Findings Prior to Diagnosis | Treatment          | Patient Observed After Treatment, Time |
|---|----------|-------------------------------------|---|-----------------------------|--------------------|--|
| Fever still indeterminate after admission of patients to clinic   |          |                                     |   |                             |                    |  |
| 1   | 67 F     | 99-103°<br>17 days                  | Rectal pain, 5 days                     | Slight tenderness           | Heat, drainage     | 2½ months                              |
| 2   | 63 M     | 99-102°<br>25 days                  | Dysuria, slight rectal pain             | Swelling                    | Incision, drainage | 3 months                               |
| 3   | 38 M     | 103°, Intermittent<br>1 year        | Intermittent chills, fever, dysuria     | Mps in rectum               | Incision, drainage | 22 days                                |
| 4   | 44 M     | 100°<br>13 days                     | Fever, slight rectal pain               | Swelling                    | Incision, drainage | 23 days                                |
| Fever, but diagnosis suspected on admission of patients to clinic |          |                                     |   |                             |                    |  |
| 5   | 52 M     | 99-101°<br>49 days                  | Chills, fever, dysuria                  | Mass, tender                | Heat (Elliott)     |  |
| 6   | 36 F     | 101°<br>8 days                      | Chills, fever, urinary retention 3 days | Nodules at anus             | Incision, drainage | 2 months                               |
| 7   | 33 M     | 99-104°<br>35 days                  | Chills, fever, urinary retention        | Retrorectal mass            | Perineal drainage  | 1 month                                |
| 8   | 42 M     | 100°<br>6 weeks                     | Chills, fever, sweats                   | Induration, right rectum    | Heat               |  |
| 9   | 22 F     | 100-101°<br>5 days                  | Malaise, fever                          | Tender anus                 | Incision, drainage | 2 months                               |
| Fever occurred post-operatively                                   |          |                                     |   |                             |                    |  |
| 10  | 55 F     | 99-102°<br>17 days<br>(1½ mo. p.o.) | Fever, rectal pain                      | Swelling                    | Incision, drainage | 1½ months                              |
| 11  | 38 F     | 99-101°<br>10 days<br>(2 wks. p.o.) | Post-operative fever                    | Induration                  | Incision, drainage | 23 days                                |

# The Intravenous Modification of the Hippuric Acid Test of Liver Function

By

R. H. MOSER, M.D., B. D. ROSENAK, M.D.\*  
INDIANAPOLIS, INDIANA

and

R. J. HASTERLIK, M.D.†  
EVANSTON, ILLINOIS

FOR several years the oral form of the Hippuric Acid Test has been a routine procedure in the study of liver cases in the Indianapolis City Hospital. The correlation of the estimation of the state of renal function by the Urea Clearance test with the excretion of the hippuric acid has been reported by Kohlstaedt and Helmer (1.) This addition to the test we consider to be of great importance. This test has been used in association with repeated determinations of the serum bilirubin, the cholesterol and ester, the plasma albumin-globulin ratio and carbohydrate tolerance tests.

In 1938 Quick introduced a modification of the hippuric acid test (2.) This consisted of the intravenous administration of 1.77 gm. of sodium benzoate and the collection of the urine for one hour after the injection. This change appears to be a definite improvement in the technic of the test because it eliminates all question of absorption and shortens the time necessary for collection of the urine specimens. The intravenous modification of the hippuric acid test has been used routinely for the past year in the Gastro-intestinal Clinic of the Indianapolis City Hospital.

While using this test certain problems arose in connection with its interpretation. One of the peculiar circumstances which has occurred is the apparent excessive excretion of hippuric acid. This phenomenon has been observed and was reported by Rosenberg at the meeting of the American Gastro-Enterological Association in May, 1941.

Although it is theoretically possible to obtain 2.2 gms. of hippuric acid from the complete conjugation of 1.5 gms. of benzoic acid, *in vitro*, nevertheless *in vivo*, the average normal amount of hippuric acid synthesized from 1.5 gms. of benzoic acid is about 1 gm. in one hour. An even greater excess of benzoic acid does not yield a proportionately greater synthesis of hippuric acid, according to Quick (4.) In our series of patients, three excreted between 2.0 and 3.5 gms. as measured by the precipitation method. Examination of the precipitate under the microscope revealed besides typical hippuric acid crystals, other crystals which resembled benzoic acid.

If the value as established by Quick, of 1.0 gm. as the average mean normal synthesis is accepted, then three possibilities exist for the synthesis of amounts greater than one gram. Firstly, as in most biological reactions, a certain number of individuals will synthesize amounts greater than the mean normal. Secondly, there is a daily endogenous excretion of hippuric acid in man of about 0.7 gm. (5.) Thirdly,

as observed by us using the precipitation method, crystals other than hippuric acid may contaminate the precipitate and yield a falsely high value. A test analyzed by the precipitation method on a patient seen in the Evanston Hospital Clinic with cirrhosis of the liver and splenomegaly proven at surgery revealed 0.86 gms. of precipitation which on microscopic examination proved to be crystals of benzoic and not hippuric acid. Obviously by this method the test would have been reported as normal, whereas in reality the patient synthesized minimal amounts or no hippuric acid, as would have been revealed by the ether extraction-formol titration method. To obviate the last mentioned error in the test, we have abandoned the use of the precipitation method in favor of the ether extraction-formol titration method. Since using this procedure, we have not encountered another case of excessive excretion and although this is a somewhat more complicated method, it seems preferable if accuracy is desired. We cannot agree with Dr. Rosenberg's conclusions that excessive excretion signifies early hepatic damage since all of his determinations were done by the precipitation method.

Another problem which must be considered in an evaluation of results of this test is that of renal excretion of the hippuric acid after its synthesis by the liver. It is well known that the kidneys may influence the synthesis as well as the excretion of hippuric acid. Mann demonstrated that synthesis of hippuric acid occurs in dogs after the removal of the liver (6.) However, from a practical clinical viewpoint, it may be accepted that most of the hippuric acid is formed in the liver. Two functions of the liver are involved in the process; first, the production of glycine and second, the conjugation of glycine with sodium benzoate. If one accepts the view that renal synthesis is a negligible factor, there still remains the question concerning the degree of excretion. There is no doubt that falsely low readings may be obtained in individuals with reduced renal function. We believe that the suggestion made by Kohlstaedt and Helmer, that a Van Slyke urea clearance be run in connection with the hippuric acid test is an important addition to the technic. This combination of tests was carried out whenever possible in our patients, when the excretion of hippuric acid was low, in an effort to differentiate between reduced synthesis with normal renal excretion and normal synthesis with reduced renal excretion. Studies on the fundamental problem of the clearance of hippuric acid by the kidney are now being made.

The patients studied by the intravenous hippuric acid test according to the technic of Quick, were divided into three groups. The first group consists of

\*From the Gastro-Intestinal Clinic of the Indianapolis City Hospital. Aided by a grant from the Eli Lilly Foundation.

†Formerly Fellow in Gastro-Enterology, Indianapolis City Hospital. Submitted September 20, 1941.



forty-five individuals seen in the gastro-intestinal clinic who excreted more than 1.0 gm. of hippuric acid. None had any present evidence of hepatic disease. One patient in this group gave a history of having had "catarrhal jaundice" in 1936 from which he had made a complete recovery. Most of the patients in this group had been operated upon for gall bladder disease. All were well at the time of examination and no other studies were indicative of hepatic dysfunction. We conclude from this group that the intravenous modification of the hippuric acid test does not give a high incidence of falsely positive results.

The remaining patients tested were placed in two groups. One consists of 31 patients who excreted less than 0.7 gm. of hippuric acid. The other consists of 26 patients who excreted between 0.7 and 1.0 grams.

An analysis of the results of the tests in these patients revealed a preponderance of proven hepatic disease in those who excreted less than 0.7 grams, whereas in those who excreted between 0.7 and 1.0 gram the incidence of proven hepatic disease was lower. The diagnoses which were made in the first group of thirty-one patients who excreted less than 0.7 grams of hippuric acid in the first hour after injection of 1.77 grams of sodium benzoate intravenously are as follows:

Eight patients in this group were diagnosed acute hepatitis. These patients were of the type ordinarily called catarrhal jaundice. We prefer the concept of this disease which is based on pathologic investigations and has established without doubt that, this condition is due to a hepatitis *per se* rather than to catarrhal cholelithiasis or duodenitis. All of these patients had periodic bilirubin determinations as well as repeated hippuric acid tests. It was well demonstrated by this group that the improvement in hepatic function as shown by the hippuric acid test was directly correlated with the serum bilirubin determinations and the clinical improvement.

Four cases of portal cirrhosis excreted less than 0.7 gram of hippuric acid. The clinic picture presented in each of these cases was typical. Three gave strong histories of alcoholism. All were found to have ascites. Three were jaundiced. Two had hemorrhages from esophageal varices. One patient was operated upon and found to have a small nodular liver. None of these patients were examined post-mortem. The excretion of hippuric acid in this group of four cases of portal cirrhosis was below 0.4 gram except one test. This test, done by the precipitation method, revealed 1.17 grams whereas tests done before and after were all below 0.4 gram. This is probably an instance of erroneous hyper-excretion, although the precipitate was not examined microscopically. The intravenous hippuric acid test is of undoubted value in diagnosis of portal cirrhosis and in our experience gave uniform results.

One case of proven hepatic disease of an unknown type was included in this group. The patient was a 33 year old colored woman, who had inadequately treated syphilis, was an acknowledged gin drinker, and had mitral stenosis. The liver was palpable four fingers below the costal border, there was a questionable ascites, and the spleen was not felt. The bilirubin was 2.1 mgs., the blood cholesterol was 266 mgs. and esters 233 mgs. On another occasion the cholesterol and ester were 333 mgs. and 288 mgs. respectively. The serum

colloidal gold was 4432100000. The urea clearance was 60% and 83%. The glucose tolerance was normal. The gall bladder did not visualize. The hippuric acid excretion was 0.28 grams as determined by ether extraction. This case was diagnosed as a chronic hepatitis. A more exact diagnosis may eventually be made, but there is no doubt that a severe degree of liver damage was present.

Another case was that of a colored man aged 52. His complaints were anorexia, weight loss, jaundice and pruritus. He was found to have a markedly enlarged, smooth, firm liver. The hippuric acid test done by the oral method was 2.53 grams. It was repeated by the intravenous method at which time the excretion was 0.5 gram. The bilirubin rose from 6.6 mgs. to 14.3 mgs. over a three months' course. The cholesterol was 227 mgm. per 100 cc. blood. The highest quantitative urobilinogen was 16.8 mgs. The gastro-intestinal X-ray was normal. The gall bladder did not visualize after a double dose of the dye. The clinical diagnosis was portal cirrhosis. At autopsy the liver weighed 4400 grams. It was finely nodular and firm. The histologic examination showed very marked periportal fibrosis with areas of regeneration. The bile channels were filled with polymorphs. The canaliculi were filled with bile plugs. The pathologic diagnosis was biliary cirrhosis. No obstructive lesion was found in the extra hepatic biliary system.

There were three cases of extensive metastases to the liver. In two of these the liver was examined at autopsy and in the other the diagnosis was confirmed by laparotomy. One case of extensive miliary tuberculosis of the liver with parenchymatous degeneration was also found at post mortem examination. The excretion of hippuric acid in each of these cases was well below 0.7 grams.

Five patients were studied following cholecystectomy. Most of these were suffering from persistent dyspepsia. The excretion of hippuric acid in this group was uniformly low. It is difficult to evaluate the significance of the reduced excretion in this type of condition. Some had other tests which were suggestive of reduced liver function. Most of the patients had more than one low hippuric acid test. In a previous paper on the subject of the dyspepsia in gall bladder disease we reported a group of patients in whom reduced hepatic function was suggested as a cause of persistent digestive symptoms. It has been established pathologically that a certain degree of hepatitis exists in many cases of gall bladder disease and it is reasonable to suppose that a decreased liver function might persist indefinitely after removal of the diseased gall bladder. However, there were a number of post-cholecystectomy patients in the control group in this study. It is, therefore, not to be concluded that all patients have diminished liver function after removal of the gall bladder since there must be varying degrees of liver damage in gall bladder disease. One patient was tested following an attack of gall bladder colic with jaundice and was found to have an excretion of 0.62 grams.

Two diabetics are included in the present group because of reduced excretion of hippuric acid. Both of these were autopsied. The first patient was a white man 48 years old. He was a severe, uncontrolled diabetic. He excreted only 0.14 grams of hippuric acid.

The urea clearance in this patient was markedly diminished and because of this the excretion of hippuric acid was not seriously regarded. However, post-mortem examination revealed marked parenchymatous and toxic degeneration of the liver.

The second diabetic was a woman of 68, who had suffered a coronary occlusion and had also had a cholecystectomy. Her out-put of hippuric acid was 0.67 gms. On post-mortem examination the liver showed marked fatty degeneration and passive congestion.

A patient with congenital hemolytic icterus following splenectomy and cholecystectomy excreted 0.58 gms. of hippuric acid on one occasion and 0.50 gms. on another. There is no pathologic proof of hepatic pathology, but it was assumed that liver damage was present in this patient.

The fact that lowered excretion of hippuric acid is found late in pregnancy has been reported. One case of this kind was encountered. This patient was at term and excreted 0.65 gms. of hippuric acid. We are making further observations on this subject.

It is assumed that in the types of clinical conditions above outlined, there exists some reason for suspecting the presence of impaired hepatic function, other than the evidence supplied by a reduced excretion of hippuric acid. In several of these cases, proof of hepatic pathology was obtained at autopsy or laparotomy. In others the clinical course was so typical as to leave no doubt as to the presence of liver disease. In a few border line cases, hepatic disease is only presumed to have been present. The question of the state of hepatic function in gall bladder disease, the post-cholecystectomy syndrome, diabetes mellitus, and pregnancy will require further investigations, but there are some evidences that impaired liver function exists in these conditions.

Three patients were found to excrete less than 0.7 gms. of hippuric acid in whom no suggestion of liver disease existed and no pathologic evidence of liver damage was obtained. Thus only three patients out of thirty-one who excreted less than 0.7 gms. had no definite evidence of liver dysfunction.

The final group of patients who are included in this study of the intravenous method of the hippuric acid test excreted less than 1.0 gram and more than 0.7 grams of hippuric acid. Of this number fifteen were patients who had been operated upon for the removal of their gall bladders. As has been previously stated it is impossible to interpret accurately the significance of this or any liver function test in such a group of patients. It must be confessed that no proof of liver damage or dysfunction can be obtained, yet it is established that in gall bladder disease a certain number of patients have hepatitis. We feel that it is only reasonable to assume that a few of these have persistent liver pathology. Most of these patients had, in addition to the intravenous hippuric acid test, a determination of the serum bilirubin, duodenal drainage, glucose tolerance test, blood cholesterol and ester and X-ray examination of the gastro-intestinal tract. Six of the fifteen were found to have no other positive tests suggestive of liver disturbance. Nine had glucose tolerance curves of the diabetic type when the Exton-Rose technic was used. One patient had an elevation of her serum bilirubin, one was found to have cholesterol crystals in the duodenal drainage bile, and a third had an abnormal plasma colloidal gold curve. We

are not able to say much about the latter test except that it has been found to be positive in many types of liver disease. We are greatly interested in the results of the glucose tolerance test. In certain instances of hepatic damage the mechanism of the liver which controls the blood sugar level is disturbed. This is apparently not a uniform change in all cases of liver disease, since it did not occur regularly in all patients with proven hepatic pathology. All that can be said conservatively about the results of the hippuric acid test in the post-cholecystectomy cases is that it is not unlikely that the cases which excreted less than 1.0 gram and certainly those who excreted less than 0.7 grams have some degree of impaired function of the liver.

Three patients were tested during attacks of gall stone colic and one during an attack of acute cholecystitis. All of these were found to have excreted less than 1.0 gram of hippuric acid. It is hypothesized that the degree of associated hepatitis in these cases was sufficient to impair the particular functions of the liver necessary for the synthesis of hippuric acid from sodium benzoate. Most of the remaining cases in this group have some definite evidence of liver disease. One was that of a colored male 20 years old who had suffered from sickle cell anemia for at least three years. He had a firm, smooth epigastric mass which at autopsy proved to be the liver. The microscopic section of the liver showed marked increase in fibrous tissue which was infiltrated with round cells. There were areas of regenerating hepatic parenchyma. The diagnosis was acute hepatitis and portal cirrhosis.

There was one case of acute hepatitis. The excretion of hippuric acid on the fourth day of illness was 0.88 grams. Six weeks later the patient excreted 1.33 grams. At this time he was practically well.

Two cases of hepatomegalia of unknown etiology are included in the present group. One patient with a marked avitaminosis and congestive heart failure with marked enlargement of the liver excreted 0.73 grams. The urea clearance in this case was 43% and one cannot regard the hippuric acid excretion too seriously, however, there is ample reason to have suspected liver dysfunction in this case.

The two remaining cases in this group had little or no evidence of liver disease. One had duodenal ulcer and the other had rheumatoid arthritis under treatment with gold. It is possible that there was some toxic hepatitis in the latter case. He excreted 0.75 grams of hippuric acid and had a normal urea clearance.

The evidence, both clinical and laboratory seemed somewhat less convincing of the presence of liver damage in this latter group than in the group which excreted less than 0.7 grams of hippuric acid. However, in practically every patient in the last group, the possibility of liver pathology existed.

We have attempted to decide whether the fixing of a lower level for the definitely pathologic excretion of hippuric acid would result in a distinctly more accurate interpretation of the test. There was in the present study a preponderance of proven cases of liver disease in the group of patients who excreted less than 0.7 grams. It is certainly conservative to state that according to our experience the excretion of less than 0.7 grams is highly indicative of liver damage if

the renal excretion is not seriously impaired, and that the excretion of between 0.7 and 1.0 gram is at least suggestive of liver dysfunction.

### CONCLUSIONS

1. The intravenous modification of the hippuric acid test according to the technic of Quick is a safe method which has the advantages of being shorter in time and more accurate from the point of view of absorption than the oral test. It is an important adjunct to the list of laboratory procedures which may be of value in the diagnosis and in checking the clinical course of various hepatic diseases, but it is not a perfect liver function test in the sense that it will reveal minimal hepatic damage.

2. The estimation of hippuric acid in the urine may be done by precipitation and weighing or by the ether extraction—Formol titration methods. The latter method is more time consuming and tedious than the former, but has the advantage of eliminating the possibility of obtaining what appears to be excessive excretion of hippuric acid which in our opinion may be due to the excretion of sodium benzoate itself.

3. We consider it of great importance to have some definite idea of the functional capacity of the kidneys before a proper interpretation of the hippuric acid test can be made.

4. There may be an advantage in placing the absolute level of pathologic excretion at 0.7 of a gram. There is little doubt that the liver is not functioning to its full capacity if the synthesis of hippuric acid is below this level when the kidneys are able to excrete the hippuric acid. Excretion of between 0.7 of a gram and 1.0 gram is suggestive of impaired liver function.

### REFERENCES

1. Kohlstedt, K. G. and Helmer, O. M.: Study of the Hippuric Acid Excretion as a Test of Hepatic Function. *Am. J. Dig. Dis. and Nutrit.*, 3:453-466, Sept., 1935.
2. Quick, A. J., Ottenstein, H. N. and Weltchek, H.: Synthesis of Hippuric Acid in Man Following Intravenous Injection of Sodium Benzoate. *Proc. Soc. Exper. Biol. and Med.*, 38:77-78, Feb., 1933.
3. Rosenberg, David: Comparison of the Cephalin-Cholesterol Flocculation Test with Various Criteria of Liver Function. Read at meeting of American Gastro-Enterological Association, May 5, 1941.
4. Quick, A. J.: The Conjugation of Benzoic Acid in Man. *J. Biol. Chem.*, 92:65-85, June, 1931.
5. Hawk and Bergel: *Practical Physiological Chemistry*. Eleventh Edition, 1937, P. Blakiston's Son & Co.
6. Mann, Frank C.: The Effects of Complete and Partial Removal of the Liver. *Medicine*, VI, 419-511, Dec., 1927.

## Etiology of Acute Pancreatitis\*†

By

H. L. POPPER, M.D.  
CHICAGO, ILLINOIS

TWO different forms of acute pancreatitis are known: the mild one, recently called transient pancreatitis; and, the severe one, pancreatic necrosis. In the transient form edema of the pancreas or a moderate degree of inflammation with varying degrees of fat necrosis is found in and around the pancreas. In the severe form the typical picture of hemorrhagic necrosis of the pancreas is present. The pathogenesis and relation of these two forms of acute pancreatitis is still controversial. A few authors believe that both are essentially the same, differing only in degree, but the majority of authors consider the transient form either as a mild inflammation or as the result of an obstruction to the outflow of pancreatic secretion. Pancreatic necrosis is generally believed to be caused by intrapancreatic activation of trypsin due to the entrance of bile into the pancreatic ducts.

Rich and Duff (1) have offered another explanation for acute pancreatitis. They assumed that metaplastic epithelium of the smaller pancreatic ducts, which they and others (2) had found to occur, could obstruct these ducts. The following retention would lead to congestion and rupture of ducts similar to that occurring in the experimental production of pancreatitis by injection of bile or other substances into a pancreatic duct. Through the ruptured ducts secretion would escape into the pancreatic tissues, causing a spreading process of acute pancreatitis.

The author has been able, however, to produce edema of the pancreas of the dog by injection of rather small amounts of bile, such as 1/10 of a cc. into a pancreatic duct with no histological evidence of rupture of ducts (3.)

A reflux of bile into the pancreas can only occur when pancreatic and common bile ducts form a common channel. Anatomists and pathologists have investigated the occurrence of such common channel formation in the average human autopsy material, but the results have been contradictory.

It seems likely that in cases of common channel formation not only a reflux of bile into the pancreas, but also a reflux of pancreatic juice into the bile passages may take place. Bile reflux into the pancreas can be revealed at necropsy only. Entrance of pancreatic juice into the bile passages is detectable during life by the detection of pancreatic enzymes in the bile.

The author has performed enzyme determinations in the aspirated gall bladder bile of 200 surgical cases (4-6.) Cases with disease of the pancreas are omitted in this series. One hundred and sixty-four of the patients were operated on for gall bladder disease, and 36 for other abdominal disease. The latter group revealed a normal bile system at operation. Pancreatic enzymes were found in the bile of 10% of all cases. That means that in these 10% a common channel was present, through which pancreatic reflux into the biliary system was made possible (7.) In recent years these results have been confirmed by several authors, who demonstrated common channel formation clinically and roentgenologically in gall bladder cases in a slightly higher percentage than in the author's series

\*Aided by the Otto Baer Fund.

†Reported at the Chicago Society of Internal Medicine, February 24, 1941.

From the Department of Gastro-Intestinal Research, Michael Reese Hospital.

Submitted September 5, 1941.

(8-11.) It seems, therefore, that common channel formation occurs in about 10% of cases with various abdominal pathology exclusive of pancreatitis. For further references see Alvarez (20.)

Although the theory of biliary reflux into the pancreas as the main etiologic factor in pancreatic necrosis has been widely accepted, the anatomical occurrence of common channel formation in pancreatitis has been neglected, and extensive anatomical investigations have not been performed. The reason for this may be the comparatively small number of cases coming to autopsy and the fact that the region of the papilla is often so much involved in the pathological process that anatomical investigation is hardly possible.

The author has tried another approach to this question by analyzing bile from cases of acute pancreatitis for the presence of pancreatic enzymes. In 16 out of 18 cases of pancreatitis, pancreatic enzymes were found in the bile (6, 12.) In other words, evidence for the existence of common channel formation between bile and pancreatic ducts was found in 89% of cases of acute pancreatitis. Six of the above sixteen cases came to autopsy. In four an anatomical common channel was found, but no signs of the presence of bile in the pancreas were apparent. In only two of the cases signs of bile could be detected in the pancreas. These observations conform with those of other authors (11, 13, 15) who likewise reported the lack of signs of an actual inflow of bile into the pancreas in the majority of cases of pancreatitis. The findings of Harms (16), Dragstedt (17) and Wolfer (18) that the secretory pressure of the pancreas usually exceeds that of the liver may explain the relatively rare occurrence of bile in the pancreas in spite of the functioning common channel. Yet the presence of a common channel in 89% of the cases of pancreatitis reported above, forces one to assume a causative relationship between common channel formation and acute pancreatitis in spite of lack of evidence of bile in the pancreas in the majority of the cases. The following mechanism seems most likely: firstly, the existence of a common channel; second, obstruction to the outflow from this common channel; thirdly, in a few cases, entrance of bile into the pancreas; in the majority of cases, however, due to the greater secretory pressure of the pancreas, entrance of pancreatic juice into the bile passages; fourth, activation of the pancreatic enzymes either within the pancreas or in the common ampulla and the bile passages; and, fifth, in case the activation took place in the bile passages, extension of the process of activation into the congested secretory ducts of the pancreas.

Fat necrosis of liver cells in a case of acute pancreatitis, apparently due to reflux of activated pancreatic juice, has been described recently by Schiller (19.)

In 3 of the above described 16 cases of pancreatitis with common channel the operation did not reveal any pathological changes in the biliary system. One of these cases came to autopsy. A normal biliary system without stones or signs of inflammation, and no sign of bile reflux into the pancreas was found. A corre-

lation between pancreatitis and bile system would have been denied categorically in this case had the presence of pancreatic enzymes in the bile not proved the presence of a common channel. This demonstrates firstly, that the finding of normal bile passages at operation or at autopsy need not exclude the possibility of causation of the pancreatitis by way of these normal bile passages; and secondly, that the presence of a normal biliary system in case of acute pancreatitis need not necessitate the assumption of an extra-biliary mechanism for the pancreatitis.

The above described cases of pancreatitis with evidence of a common channel included mild forms of pancreatitis as well as cases with hemorrhagic necrosis. Nevertheless, in 89%, pancreatic enzymes were found in the bile. This suggests that the mild as well as the severe forms of pancreatitis are of the same etiology. It seems probable, that in both forms of pancreatitis we are dealing only with different degrees and stages of pathology and with different reactions to a common causative mechanism.

### SUMMARY

1. Presence of a common channel between common bile duct and pancreatic duct was found in 16 out of 18 cases of acute pancreatitis. In the majority of these cases pancreatic juice had entered the bile passages, but only in a few of them had bile entered the pancreas.
2. In most cases of acute pancreatitis activation of pancreatic enzymes occurs in the common ampulla and in the biliary passages and is assumed to extend into the pancreas.
3. In three cases of pancreatitis with normal bile passages a reflux of pancreatic juice into the bile passages was found. The finding of a normal biliary system in cases of pancreatitis does not necessitate the assumption of another causative mechanism besides the common channel.
4. Evidence of a common channel was found in mild forms of pancreatitis as well as in pancreatic necrosis. This indicates that the different types of acute pancreatitis may be caused by the same pathogenetic mechanism.

The author is indebted to Dr. H. Necheles for help and advice.

### REFERENCES

1. Rich, A. R. and Duff, G. L.: *Bull. Johns Hopkins Hosp.*, 58:212, 1936.
2. Priesel, H.: *Frankfurter Zeitschr.*, 26:453, 1922.
3. Popper, H. L.: *Surgery*, 7:566, 1940.
4. Popper, H. L.: *Wiener Klin. Wochn.*, 42:800, 1929.
5. Popper, H. L.: *Medizinische Klinik*, 25:1248, 1929.
6. Popper, H. L.: *Arch. f. klin. Chir.*, 175:660, 1933.
7. Popper, H. L.: *Zbl. Chir.*, 57:1590, 1930.
8. Colp, R. and Doubilet, H.: *Ann. Surg.*, 108:243, 1938.
9. Colp, R. and Doubilet, H.: *Surg.*, 4:837, 1938.
10. Leven, N. L.: *Proc. Soc. Exper. Biol.*, 38:808, 1938.
11. Robins, S. A. and Hermanson, L.: *S. G. and O.*, 62:684, 1936.
12. Popper, H. L.: *Wiener Klin. Wochn.*, 47:295, 1934.
13. Marcus, Verhdlg. Ges. Verdauungs Krkh., 1924, 4. Tagung.
14. Borchardt, M.: *Verhdlg. Ges. Verdauungs Krkh.*, 1924, 4. Tagung.
15. Guleke, N.: *Arch. Klin. Chir.*, 148:69, 1927.
16. Harms, E.: *Arch. Klin. Chir.*, 147:637, 1927.
17. Dragstedt, L. R., Haymond, H. E. and Ellis, I. C.: *Arch. Surg.*, 28:232, 1934.
18. Wolfer, J. A.: *S. G. O.*, 53:433, 1931.
19. Schiller, W.: *S. G. O.*, 72:70, 1941.
20. Alvarez, W. C.: *An Introduction to Gastro-Enterology, Bile Ducts. Third Edition of Mechanics of the Digestive Tract.* Paul B. Hoeber, Inc., 1940.

## Fear and Gastric Acidity

By

FREDERICK HOELZEL  
CHICAGO, ILLINOIS

MY impression during the past was that the role of psychic factors and particularly of sexual maladjustments in gastro-intestinal disorders was grossly exaggerated but the editorial concerning peptic ulcer in war time by B. B. Crohn in the September issue of the American Journal of Digestive Diseases (8:359, 1941) and the article on digestive disorders in soldiers by Hurst in the same issue lead me to report the accidental observation of a doubling of my fasting gastric acidity by a situation involving the fear of being shot. This occurred during a period (1925 to 1929) in which I made routine daily determinations of my fasting gastric acidity. Over 3000 determinations were made before January 4, 1928, when the otherwise relatively smooth flow of events in my environment was disturbed by an attempted robbery in the house in which I then lived. In the course of this robbery attempt, my landlady was shot. I was naturally upset as I happened to be in another part of the house when the shooting occurred but I remained upset after that because I was responsible for the arrest of the culprits who were directly involved and I then feared that I might be shot by their friends. Ten days after the shooting, I moved to a location where I felt entirely safe and my fasting gastric acidity then dropped to a level below what I previously regarded as my normal.

Earlier observations on my fasting gastric acidity showed that this varied with the periodic gastric motility (Am. J. Physiol., 73:463, 1925) and with the protein intake (Am. J. Physiol., 77:166, 1926.) However, about the time my landlady was shot, my protein intake was fairly constant and relatively high and the free acid of the fasting gastric contents ranged be-

tween 0 and 0.13%. On the morning after the shooting, it was 0.26% and it remained above 0.17% until after I moved. Then free acid was often absent and a level of 0.13% was not reached again for several weeks. The finding of the striking increase in the fasting gastric acidity came as a surprise to me. The discovery was made in going through a morning routine in which the making of at least one gastric aspiration had become as regular a feature as washing the hands and face. It was only after finding my gastric acidity doubled that I would have been willing to admit that I was definitely upset and feared being shot. Fear such as I then experienced is evidently felt by many individuals in bombed or war-torn areas.

That a fasting gastric acidity of 0.17% to 0.26% might produce ulceration or hemorrhage, particularly when the diet is deficient in protein and/or fat, was indicated by the experiences which led to one of my reports (in the A. J. P., 77:166.) A free acidity of the fasting gastric contents of 0.26% was then reached only after prolonged protein restriction or protein starvation. At such times, the stomach or lower part of the esophagus often began to bleed from the suction involved in trying to make thorough aspirations. Further observations then had to be temporarily stopped and/or the diet changed because of a burning feeling from sites (apparently mainly at the cardia) injured by the acid gastric juice. A flaring up of old peptic lesions or the development of new ones in some individuals under such circumstances therefore seems easily conceivable. However, I would like to add that it would be regrettable if a report like the foregoing led to a neglect of the possible physical bases of peptic ulceration and the possible physical bases of emotional disturbances like fear.

Submitted September 20, 1941.

## A Vitamin Survey of Normal Industrial Workmen\*

By

J. G. SCHNEDORF, M.D., Ph.D., C. J. WEBER, M.D., Ph.D.

and

LOGAN CLENDENING, M.D.  
KANSAS CITY, KANSAS

EXPLOITATION of the vitamins, both commercially and professionally is without rival. The rapidly expanding literature upon this subject has changed from reports of the signs and symptoms of the relatively few cases of frank avitaminosis to an emphasis, with a growing alarm, upon the prevalence of "subclinical" vitamin deficiency disease throughout

the country. Many of these reports deal with endemic vitamin deficiency and with vitamin deficiency in hospital patients who are ill. A survey of healthy men engaged in industrial work is therefore appropriate because the presence of mild forms of vitamin deficiency disease among them might seriously interfere with the industrial output of our country.

This paper reports the results of a vitamin survey of 1265 healthy men between the ages of 20 and 65

\*From the Hixen Laboratory of Medical Research, University of Kansas School of Medicine.  
Submitted September 15, 1941.



who are engaged in industrial labor. Physical examination for the signs of vitamin deficiency was done upon all of them, and detailed dietary histories were obtained upon 300 of them. Blood plasma Vitamin C determinations were done according to the method of Mindlin and Butler (1) in 78 cases, and correlated with the Vitamin C intake in the diet and the signs of Vitamin C deficiency.

## RESULTS AND DISCUSSION

**Vitamin A:** The 1265 men were examined for xerophthalmia and for the keratotic papules upon the skin

TABLE I

### *Avitaminosis survey of industrial workmen*

|   |                               |
|---|-------------------------------|
| <b>I. Dietary Habits (300 histories)</b>  |                               |
| 1. Glasses of milk a week:  |                               |
| 23 .....  | none                          |
| 277 .....   | 6 to 28 glasses               |
| 2. Eggs a week:   |                               |
| 300 .....   | 2 to 24 eggs a week           |
| 3. Citrus fruits (oranges, lemons, limes, grapefruit and tomatoes):                         |                               |
| 27 .....  | none                          |
| 66 .....  | 1+                            |
| 95 .....  | 2+                            |
| 56 .....  | 3+                            |
| 56 .....  | 4+                            |
| 4. Oatmeal:   |                               |
| 140 .....   | none                          |
| 36 .....  | occasional                    |
| 124 .....   | moderate                      |
| 5. Bread:   |                               |
| 63 .....  | whole wheat                   |
| 101 .....   | white                         |
| 136 .....   | whole wheat and white and rye |
| 6. Carrots:   |                               |
| 26 .....  | none                          |
| 274 .....   | +                             |
| 7. Corn:  |                               |
| 35 .....  | none                          |
| 265 .....   | +                             |
| 8. Squash:  |                               |
| 172 .....   | none                          |
| 138 .....   | +                             |
| 9. Sweet Potatoes:  |                               |
| 45 .....  | none                          |
| 255 .....   | +                             |
| 10. Spinach:  |                               |
| 36 .....  | none                          |
| 274 .....   | +                             |
| <b>II. Possible Defective Absorption: No cases</b>  |                               |
| 1. Indigestion:   |                               |
| 246 .....   | none                          |
| 52 .....  | +(gas, heartburn, dyspepsia)  |
| 2. Peptic Ulcer:  |                               |
| 2 cases .....   | healed                        |
| 3. Biliary Disease:   | none                          |
| 4. Diarrhoea:   | none                          |
| 5. Teeth:   |                               |
| 73 .....  | bad (sepsis, snags, loss)     |
| 37 .....  | fair                          |
| 36 .....  | plates                        |
| 154 .....   | good                          |
| <b>III. Physical Signs and Symptoms (1265 cases)</b>  |                               |
| 1. Vitamin A:   |                               |
| a. Keratotic papules upon skin of thighs, arms and shoulders .....                          | none                          |
| b. Attacks of boils .....   | 4                             |
| c. Folliculitis .....   | 2                             |
| d. Xerophthalmia .....  | none                          |
| e. Night blindness .....  | none                          |
| 2. Vitamin B Complex:   |                               |
| a. Muscle pains, paresthesia, polyneuritis .....  | none                          |
| b. Pigmented dermatitis (sock, glove or necklace type, scurfiness of skin over knees) ..... | none                          |
| c. Diarrhoea .....  | none                          |
| d. Cheilosis .....  | none                          |
| e. Conjunctivitis .....   | none                          |
| 3. Vitamin C:   |                               |
| a. Sore tongue, swollen bleeding gums .....   | none                          |
| b. Joint hemorrhages .....  | none                          |
| c. Edema .....  | none                          |
| d. Hyperkeratotic skin papules .....  | none                          |
| e. Delayed wound healing .....  | none (in 50 wounds)           |
| f. Blood plasma level .....   | see Table II                  |
| 4. Vitamin D:   |                               |
| a. Pigeon breast and beading ribs .....   | one instance                  |
| 5. Vitamins E and K:  | no observations               |

of the thighs, arms and shoulders which were thought to be specific for Vitamin A deficiency (2, 3.) Scheer and Keil (4) however, report papules of Vitamin C deficiency which resemble those of Vitamin A deficiency very closely. In addition each man was questioned for a history of night blindness. While night blindness has been accepted as a sign of Vitamin A lack, the use of the photometer for the determination of dark adaptation as an index of Vitamin A deficiency has been questioned (5.)

The dietary history of 300 men revealed that 24 of them might have an inadequate Vitamin A intake because their diet was deficient in carrots, sweet potatoes, spinach, corn, milk, butter and eggs. However, no cases of xerophthalmia, night blindness or specific dermatosis were noted. In this group several cases of folliculitis were found, but these were attributed to their greasy occupation. The absence of Vitamin A deficiency disease among these men is not surprising in view of the fact that only a few cases of xerophthalmia have been reported in this country (6) and the number of cases of outspoken night blindness was very small in the questionnaire survey of a group of ophthalmologists (7.)

**Vitamin B Complex:** A blood test for the determination of Vitamin B<sub>1</sub> (8) and urine tests for nicotinic acid (9, 10, 11) have been developed but have not been used extensively. Specific diagnostic methods for riboflavin and Vitamin B<sub>6</sub> are not available as yet. Normal values for the metabolism of these vitamins in humans are also to be determined yet.

History of muscle pains, paresthesia or polyneuritis suggesting Vitamin B deficiency was negative. Defective absorption has been assigned as a cause of avitaminosis. In this series, inquiry was made as to the presence of digestive disturbances as a reason for defective absorption. Indigestion (gas, heartburn or dyspepsia) was present in 52 of the 300 cases. History of a healed peptic ulcer was obtained in two instances. Diarrhoea and biliary disease did not occur in any instance. In no instance was the digestive disturbance sufficient to result in B deficiency from defective absorption.

No cases of pigmented dermatitis, soreness of the mouth, redness of the tongue, indigestion, diarrhoea and disturbances of the nervous system suggesting subclinical pellagra (12) were seen in any of the 1265 men examined.

Cheilosis and conjunctivitis reported to be indicative of endemic riboflavin deficiency by Spies et al (13) also were not observed in any of the men.

**Vitamin C:** Munsell (14) reported that a normal Vitamin C balance is maintained adequately in the normal adult by an average daily ascorbic acid intake of 40-60 mg. and that an intake of 80 mg. is sufficient for all needs. In terms of citrus fruits this is roughly equivalent to either 2 oranges, 2 lemons, 2 limes, one-half grapefruit or 3 tomatoes each day. With their chemical test for the determination of reduced ascorbic acid in the blood plasma, Farmer and Abt (15) have reported that Vitamin C values less than 0.75 to 0.80 mg. per cent indicate a subnormal Vitamin C intake. They state that active scurvy may occur with values ranging up to 0.4-0.5 mg. per cent.



The results of our blood plasma studies (Table II) show that only 13 of the 78 normal workmen (15.3 per cent) had a blood Vitamin C level greater than 0.75 mg. per cent. Subnormal blood plasma levels between 0.5 and 0.75 mg. per cent occurred in 15 instances (19.2 per cent) while levels compatible with those found in scurvy occurred in 50 cases (64.1 per cent.) An analysis of the dietary records of these cases indicates that only 14 (17 per cent) of the 78 gave a history of eating an average of one or more citrus fruits and 2 tomatoes daily; additional Vitamin C was derived from non-citrus foods in the diet. Fifteen (19 per cent) of the men ate an average of 5 oranges and 10 tomatoes a week. Forty-nine (62 per cent) of the workmen were grossly deficient in their dietary intake of Vitamin C according to present standards, and 7 reported that they did not average 1 citrus fruit or 1 tomato per week.

The blood plasma Vitamin C level of these men roughly paralleled their dietary intake of Vitamin C. This confirms the impressions of other workers (16, 18, 19.)

Although 7 of the men reported that they did not average 1 citrus fruit or 1 tomato a week, all of them

TABLE II

*Blood plasma Vitamin C in 78 normal industrial workmen and its relationship to the dietary intake of ascorbic acid*

| Intake Per Week |              | No. of Cases | Plasma Vitamin C mgm. % | No. of Cases | Clinical Signs of Scurvy |
|-----------------|--------------|--------------|-------------------------|--------------|--------------------------|
| Citrus Fruits   | Tomatoes     |              |                         |              |                          |
| Less than 2     | Less than 4  | 24           | 0.1-0.25                | 31           | 0                        |
| Less than 3     | Less than 6  | 25           | 0.25-0.50               | 19           | 0                        |
| Less than 5     | Less than 10 | 15           | 0.50-0.75               | 15           | 0                        |
| 7 or more       | 14 or more   | 14           | 0.75-1.75               | 13           | 0                        |

had traces of Vitamin C in their blood plasma. It is possible that the human body can synthesize Vitamin C as is suggested by Rohmer et al (20) from their studies upon infants under 5 months of age. Their evidence for this presumption was the fact that the babies examined by them continued to excrete cevitamic acid in the urine for 48 hours after they had been on a "scurbutic" diet. The data of Abt and Farmer (16) and of Crandon et al (21) however demonstrate that a much greater time is required for the complete depletion of the Vitamin C stored in the tissues when the diet contained no Vitamin C. It took 41 days upon a diet free from Vitamin C (no milk, fruit or vegetables of any kind) before the blood plasma fell to zero in the human experiment of Crandon (21) while the white cell platelet ascorbic acid did not reach zero until the eighty-second day of the diet. Probably the greatest source of the plasma Vitamin C in these 7 men was from milk and other fruits and vegetables in their diet.

Signs or symptoms of scurvy were not present in any of the 50 men with plasma Vitamin C levels under 0.5 mg. per cent nor were any signs of "subclinical" scurvy observed in the 15 men whose blood levels ranged from 0.5 mg. to 0.75 mg. per cent.

None of the 1265 men examined showed any clinical

signs of scurvy such as the specific hyperkeratotic skin papules (3, 21), hemorrhages, sore and swollen joints, bleeding gums, weakness and edema. No instance of delayed healing or disruption of the wound occurred in any of 50 cases in which traumatic lacerations and operative wounds were sutured.

The literature contains only one report of the carefully controlled production of experimental scurvy in the human (Crandon et al, 21.) The first signs of Vitamin C deficiency to develop were hyperkeratotic papules on the skin. These, however, did not develop until after the human subject had been on a diet totally deficient in Vitamin C for 132 days and after the plasma Vitamin C level had been zero for 13 weeks. Perifollicular hemorrhages of scurvy did not develop before 161 days of the diet and after a plasma level of zero had been present for 17 weeks. They also observed normal wound healing after 3 months of Vitamin C deficiency when the plasma ascorbic acid had been zero for as long as 44 days. They observed no gross changes in the gums or the teeth although X-ray films showed interruptions of the lamina dura. No evidence of lowered resistance to infection was observed.

Eighty-five per cent of the 78 normal men we have studied had a "subnormal" plasma Vitamin C level (less than 0.75 mg. per cent) and 64 per cent of them had what was formerly thought to be a dangerously low level (17, 22) of less than 0.5 mg. per cent. In addition, the diets of some of them suggested that they might be deficient in their intake of other vitamins. Yet none of them showed any of the signs or symptoms of scurvy. These observations, together with the observations of Crandon et al, suggest that the blood plasma cevitamic acid level is a poor index of the Vitamin C status of the patient. They also suggest that the daily requirements for normal human adults are too high, since they are based upon the assumption that tissue and plasma saturation is necessary for normal good health. This presumption is not supported by experimental evidence upon humans and by our studies. The majority of our men had blood plasma Vitamin C levels far below the saturation level, and yet none of them showed any signs of scurvy or impaired health.

Recent publications of studies of the blood plasma ascorbic acid levels in normal humans and patients suggest that plasma levels below 0.5 mg. per cent are frequent and are compatible with good health. Bryan et al (18) report that the plasma ascorbic acid level in healthy human subjects depended upon the Vitamin C intake in the diet and ranged from less than 0.1 to 1.3 mg. per cent with almost half of the subjects with a level under 0.5 mg. per cent. Croft and Snorf (19) could not find any definite signs of scurvy other than gingival sepsis and caries in 38 of their series of 100 unselected patients who had a plasma ascorbic level below 0.4 mg. per cent. Although Bartlett et al (22) view a blood plasma level below 0.5 mg. with alarm and regard values between 0.5 mg. and 0.8 mg. per cent as subnormal, they report no signs of scurvy in any of the 125 patients who had a plasma level less than 0.5 mg. per cent. The control group of 120 normal healthy medical students reported by Rhinehart et al (23) had a range of plasma Vitamin C of 0.22 mg. to 1.45 mg. per cent. Of this group 26.6 per

cent were below 0.5 mg. per cent and 4.2 per cent were below 0.3 mg. per cent and yet none of them showed any signs or symptoms of scurvy. In view of this evidence, the low values observed in the absence of clinical signs of scurvy can not be regarded as "sub-normal."

**Vitamin D:** We found only one instance of rickets during childhood in a man who had a pigeon breast and beading of the ribs.

**Vitamin E and K:** No significant observations were made relative to the Vitamin E and K status of the workmen examined.

#### SUMMARY

We have examined 1265 healthy adult men engaged in industrial work for evidence of vitamin deficiency disease. A detailed dietary and symptomatic history revealed that 24 out of 300 had a diet inadequate in Vitamin A. However, no instance of subclinical Vitamin A deficiency was observed. No instance of xerophthalmia, night blindness or hyperkeratotic skin plaques was observed in any of the 1265 men.

No cases of muscle pains, paresthesia, polyneuritis suggesting Vitamin B<sub>1</sub> deficiency were seen. Gastrointestinal symptoms (gas, heartburn and dyspepsia) were reported by 52 of the 300 questioned, but none of these were severe enough to cause a defective Vitamin B absorption nor could they be conclusively attributed to Vitamin B<sub>1</sub> deficiency.

No cases of pigmented dermatitis, soreness of the

mouth, redness of the tongue, indigestion, diarrhoea and disturbances of the central nervous system suggesting subclinical pellagra were seen.

The cheilosis and conjunctivitis characteristic of riboflavin deficiency were not seen.

Blood plasma ascorbic acid determinations upon 78 of the normal workmen showed that only 13 (15 per cent) of them had a level over 0.75 mg. per cent, while 64 per cent of them had plasma levels below 0.5 mg. per cent. The blood plasma ascorbic acid level correlated with the dietary intake of Vitamin C. None of the men showed any signs or symptoms of Vitamin C deficiency and all of them enjoyed good health and were physically able to do industrial work. These observations, together with others in the literature, indicate that plasma cevitamic acid saturation is not necessary for good health and that signs of scurvy will not develop even with plasma levels ranging from 0.1 mg. to 0.5 mg. per cent. Conversely there is no well-controlled experimental evidence upon human subjects which proves that tissue and plasma ascorbic acid saturation is necessary for normal good health. The estimated daily requirement of cevitamic acid therefore is considerably less than the 60-80 mg. advocated, and these smaller amounts in the diet are compatible with good health. The increasing number of reports upon the wide-spread prevalence of vitamin deficiency disease and its deleterious effect upon health should therefore not be viewed with too great alarm.

#### REFERENCES

1. Mindlin, R. L. and Butler, A. M.: "Determination of Ascorbic Acid in Plasma, Micromethod and Micromethod." *J. Biol. Chem.*, 122:673, 1938.
2. Frazier, C. N. and Hu, C. K.: "Cutaneous Lesions Associated with Deficiency in Vitamin A in Man." *Arch. Int. Med.*, 48:507, 1931.
3. Youmans, J. B. and Corlette, M. B.: "Specific Dermatoses Due to Vitamin A Deficiency." *Am. J. Med. Sci.*, 195:644, 1938.
4. Scheer, M. and Kell, H.: "Follicular Lesions in Vitamin A and C Deficiencies." *Arch. Dermat. and Syph.*, 30:177, 1931.
5. Jung, F. T. and Isaacs, B. L.: "The Measurement of Vitamin A Deficiency in Man." *Proc. Inst. Med. of Chicago*, 1939.
6. Thorson, J. A.: "Nutritional Xerophthalmia." *J. A. M. A.*, 103:1438, 1934.
7. Hess, A. F. and Kerley, D. B.: "Incidence of Xerophthalmia and Night Blindness in the United States. Gauge of Vitamin A Deficiency." *Am. J. Pub. Health*, 23:935, 1933.
8. Meiklejohn, A. P.: "The Estimation of Vitamin B<sub>1</sub> in Blood by a Modification of Schopfer's Test." *Biochem. J.*, 31:1441, 1937.
9. Baudier, E.: "Quantitative Estimation of Nicotinic Acid in Urine." *Biochem. J.*, 33:1787, 1939.
10. Harris, L. J. and Raymond, W. D.: "Assessment of the Level of Nutrition. A Method for the Estimation of Nicotinic Acid in Urine." *Biochem. J.*, 33:2037, 1939.
11. Vilter, S. P., Spies, T. D. and Matthews, A. P.: "A Method for the Determination of Nicotinic Acid, Nicotinamide, and Possibly Other Pyridine-like Substances in Human Urine." *J. Biol. Chem.*, 125:85, 1938.
12. Spies, T. D., Vilter, R. W. and Ashe, W. F.: "Pellagra, Beriberi, and Riboflavin Deficiency in Human Beings; Diagnosis and Treatment." *J. A. M. A.*, 113:931, 1939.
13. Spies, T. D., Beau, W. B., Vilter, R. W. and Huff, N. E.: "Endemic Riboflavin Deficiency in Infants and Children." *Am. J. Med. Sci.*, 200:697, 1940.
14. Munsell, H. E.: "Planning the Day's Diet for Vitamin Content." *J. Am. Diet. Ass'n.*, 15:539, 1939.
15. Farmer, C. J. and Abt, A. F.: "Determination of Reduced Ascorbic Acid in Small Amounts of Blood." *Proc. Soc. Exper. Biol. and Med.*, 34:146, 1936.
16. Abt, A. F., Farmer, C. J. and Epstein, I. M.: "Normal Ceitamic (Ascorbic) Acid Determination in Blood Plasma and Their Relationship to Capillary Resistance." *J. Ped.*, 8:1, 1936.
17. Abt, A. F. and Farmer, C. J.: "Vitamin C: Pharmacology and Therapeutics." *J. A. M. A.*, 111:1555, 1938.
18. Brynn, A. H., Turner, D. F., Huenemann, R. L. and Lotwin, G.: *Am. J. Med. Sci.*, 202:77, 1941.
19. Croft, J. D. and Suor, L. D.: "Cevitamic Acid Deficiency; Frequency in a Group of 100 Unselected Patients." *Am. J. Med. Sci.*, 198:403, 1939.
20. Rohmer, P., Sanders, U. and Bezssuuff, U.: "Synthesis of Vitamin C by the Infant." *Nature*, London, 134:142, 1934.
21. Crandon, J. H., Lund, C. C. and Dell, D. B.: "Experimental Human Scurvy." *N. Eng. J. Med.*, 223:353, 1940.
22. Bartlett, M. K., Jones, C. M. and Rynn, A. E.: "Vitamin C Studies on Surgical Patients." *Ann. Surg.*, 111:1, 1940.
23. Rhinehart, J. F., Greenberg, L. D., Baker, F., Mettler, S. K., Bruckman, F. and Choy, F.: "Metabolism of Vitamin C in Rheumatoid Arthritis." *Arch. Int. Med.*, 61:537, 1938.

## Superficial Ulcerative Gastritis Following Triarsamide Therapy for Syphilis

By

I. H. EINSEL, M.D.  
CLEVELAND, OHIO

THE gastric upset associated with certain toxic states frequently involves pathological changes which ordinarily escapes detection. The following case emphasizes this fact and proves that a gastroscopic examination may demonstrate superficial ulcerative gastritis resulting from triarsamide medication for syphilis. Apparently such an observation has not previously been reported.

Submitted September 30, 1941.

#### CASE REPORT

B. H., male, 43, referred by Dr. Vigor of Brecksville, Ohio, had heavy anti-luetic treatment followed by uncontrollable vomiting of several weeks' duration. Syphilis was acquired many years previously but was untreated until central nervous system involvement supervened in 1933. He then received neosarsphenamine, bismuth and mercury therapy intermittently during the following five years. Late in 1938 triarsamide was administered; four injections of 1 gm. and two of 2 gm. each. Severe gastric

distress and nausea gradually supervened and then gradually disappeared.

### EXAMINATION

X-ray examination, made two weeks after stopping triparamide therapy, showed the gastro-intestinal tract normal except for thick gastric rugae, deep gastric peristaltic waves starting close to the esophagus and slight spasm of descending colon. Gall bladder visualization with the dye was good. Gastroscopic examination in three depths showed pyloric sphincter normal, the angulus was edematous with occasional superficial eroded areas. The gastric corpus contained

hundreds of eroded areas 2 to 4 mm. in diameter with a pearly white base and red edge. The lesions were chiefly on the anterior and posterior wall and the greater curvature but were relatively scarce on the lesser curvature and at the cardiac end of the stomach. The mucosa was edematous and bled easily when touched by the gastroscope.

A second gastroscopic examination seven months later showed the gastric mucosa normal except for a slight edema which probably resulted from taking 30 grs. of acetylsalicylic acid for a severe headache the day before.

## Gastrojejuno-Colic Fistula\*

By

JUSTIN J. STEIN, M.D., F.A.C.S.†  
JANES, ILLINOIS

THE successful treatment of gastrojejuno-colic fistula is practically always of a surgical nature. The patients generally become anemic and debilitated as a result of the nutritional disturbances brought about by the inability of the small intestines to assimilate an adequate diet. Also Pfeiffer (1) has pointed out that the continued entrance of colon contents into the upper gastro-intestinal tract is a very serious complication.

The purpose of this paper is to briefly discuss the general considerations of gastrojejuno-colic fistula, to report a successfully treated case, and to stress the importance of performing the operation in multiple stages. Since the surgical procedure consists in removing the gastroenteric stoma, closure of the colonic and jejunal fistulae, and re-establishment of gastro-intestinal continuity, the operative mortality will be greatly reduced by multiple stage operations.

### ETIOLOGY

Since gastrojejuno-colic fistulas generally follow jejunal ulcers which develop after gastro-enterostomy, the etiological factors are essentially the same as those causing post-operative jejunal ulcer.

Hyperacidity, the application of tight intestinal clamps, the use of non-absorbable suture material, improper post-operative care, and other factors have been prominently mentioned as the causative agents for post-operative jejunal ulcer. Careful studies by different investigators have proven that these factors may be of some importance but that they have been greatly exaggerated since the ulcers occur where clamps have not been applied, absorbable suture material used, and a low gastric acidity is present. Errors in surgical technique, such as improper location of the anastomosis, sharp angulation of the proximal and distal loops of the jejunum at the site of anastomosis, and placing the sutures too close together in the mucosa, must not be minimized. Perhaps an inherited

constitutional predisposition to form ulcer or an ulcer diathesis is the most important single factor since jejunal ulcers may develop under ideal conditions and in the best of hands. Primary jejunal ulcer is rare, whereas post-operative jejunal ulcer is relatively common. As far as is known at the present time, the etiology of gastrojejunal ulcer is purely hypothetical.

### AGE AND SEX

In the ninety-five cases collected by Verbrugge (2), one of the patients was a female. In the series of fifty cases of gastrojejuno-colic fistula and seventeen cases of impending fistula reported by Walters and Clagett (3), only one was a female. Rife (4) reported two females in his series of fourteen cases. Eusterman (5) places the proportion of males to females having gastric and duodenal ulcers as 3:1 and those with jejunal ulcers as 6:1. It can therefore be readily assumed that gastrojejuno-colic fistula is a rare or unusual complication in the female sex. It is interesting to note that in a study of one hundred and fifty cases of gastrojejunal ulcer by Walters and Clagett, only three of the patients were women.

The average age in the fourteen patients in Rife's series was 46 years. The youngest patient was 31, and the oldest 72. In the series of fifty cases reported by Walters and Clagett, five were between 20 and 30, twenty-five between 40 and 50, and only two between 60 and 70.

### INCIDENCE

In a series of 6,214 gastro-enterostomies done at the Mayo Clinic prior to January, 1924, Verbrugge reported that eighty-eight, or 1.41 per cent developed gastrojejunal ulcer. A gastrojejuno-colic fistula developed in ten, or 11.36 per cent of the eighty-eight cases and in only 0.16 per cent, of the 6,214 cases in which gastro-enterostomy was performed. Walters and Clagett reported that gastrojejuno-colic fistula was present in twenty-three, or 13.6 per cent, or 169 cases of gastrojejunal ulcer in which operation was performed in the years 1933 to 1936 inclusive. Allen (6) found the incidence of gastrojejuno-colic fistula to be 14 per cent in thirty-six cases of gastrojejunal ulcer.

\*Presented at the Surgical Section, Veterans Administration Facility, Bloomington, Illinois.

†Published with the permission of the Medical Director of the Veterans Administration. This article is for informational purposes only and does not constitute a recommendation by the author.  
†Presented at the U. S. Naval Hospital, San Diego, California.  
Submitted October 27, 1937.

Lahey (7) states that the probable incidence of gastrojejunal ulcer following gastro-enterostomy for peptic ulcer is about 15 per cent. He bases his opinion on a series of cases reported by different authors. The incidence of post-operative jejunal ulcer is reported in the literature as varying from a low of 1.4 per cent to a high of 35 per cent.

Only a few gastrocolic fistulas were reported before surgical procedures on the stomach were instituted. Zweig (8) collected seventy cases from the literature up to 1900. These cases generally occurred spontaneously from cancer of the stomach or colon. Haller (9) reported the first case in 1755. The first cases of gastrocolic fistula following gastro-enterostomy were reported by Czerny (10) in 1903.

### PATHOLOGY

As has been previously stated, a post-operative jejunal ulcer (marginal) develops with an associated inflammatory reaction about it. Because of its location and proximity to the transverse colon and the perforating tendency of jejunal ulcers, the colon becomes firmly attached in the anastomatic region. The perforating jejunal ulcer is then in a position to penetrate the different layers of the colon and eventually communicate with its lumen, forming a fistulous tract which connects the stomach, jejunum, and transverse colon. Following the development of the fistula, very little, if any, pain persists, indicating that healing of the jejunal ulcer has taken place. The distal loop of jejunum becomes dilated and the wall hypertrophied as a result of the gastric juice and fecal material from the colon being emptied into it. If the fistulous opening is large and a valve-like action is not effected by the jejunal mucosa, undigested food particles will pass through the colon. If a large degree of inflammation with subsequent scarring takes place in the colon, a low grade obstruction may develop in the transverse colon. At operation, adhesions will be noted in the anastomatic region and a firm, indurated niche can often be palpated between the jejunum and colon.

### SYMPTOMS

The characteristic picture is that of an individual who has had a duodenal ulcer which has been treated by a posterior gastro-enterostomy. Later severe pain develops which is located in the lower epigastric region near the midline and which may not respond to medical treatment, as well as the original pain noted prior to operation. This indicates the formation of a marginal or post-operative jejunal ulcer. After the jejunal ulcer has perforated into the colon forming a fistulous tract, the pain disappears since the jejunal ulcer heals, leaving a fistulous tract.

After the development of the fistula, a persistent or intermittent diarrhea takes place. The diarrhea generally comes on immediately after eating, especially if liquids are taken. The patient loses weight rapidly and, in general, becomes poorly nourished and debilitated. The patient will have eructations of a fecal odor and occasionally fecal vomiting. Although his appetite may continue to be good for some time, the fetid odor to his breath greatly discourages him to eat. As a result of the nutritional disturbance caused by the fistula, the patient becomes anemic, weak, and his resistance low.

The outstanding symptoms are therefore persistent

or intermittent diarrhea, marked loss of weight and strength, very little, if any, pain, and feculent eructation or vomiting.

### CLINICAL DIAGNOSIS

The taking of a careful history is of paramount importance and the diagnosis can generally be made from this. The history of duodenal ulcer, posterior gastro-enterostomy, later symptoms of jejunal ulcer, followed by diarrhea, fecal eructations, little or no pain, and marked loss of weight are almost diagnostic of the condition. The diagnosis can then be confirmed best by a barium enema examination demonstrating the fistulous tract. If the tract is quite small, it may be difficult to demonstrate the opening. Because of the valve-like action which exists between the colon and jejunum caused by the folds of jejunal mucosa, it is difficult to demonstrate the opening by gastro-intestinal roentgenographic examination. Occasionally undigested food particles may be seen in the stool shortly after eating.

### TREATMENT

Medical treatment—All cases should receive medical management and if the pain, diarrhea, or other symptoms persist, then surgery must be resorted to without further delay. Four to six weeks should suffice as a reasonable period of medical observation.

Surgical treatment—Since these patients are generally in very poor condition, no routine method of surgical treatment can be stated as applicable to all cases. In the case reported in this paper, a high caecostomy was performed first. Following this the patient gained one pound in weight each day for forty days, and his general condition was markedly improved. He was then explored through a left upper rectus incision and a large gastrojejuno-colic fistula found. A fairly large inactive duodenal ulcer was noted but with no obstruction. The fistulous tract was completely excised and the openings in the colon, jejunum, and stomach, closed. An anterior gastro-enterostomy was then done. As a final stage the caecostomy was closed. The convalescence was entirely uneventful. It is not believed that the patient could have survived a more formidable procedure, especially if the preliminary caecostomy had not been done.

In the great majority of cases, the gastrojejunal ulcers follow gastro-enterostomy for duodenal ulcer. This is probably because of the high degree of gastric acidity encountered with duodenal ulcers, since gastrojejunal ulcer or fistula is very rare in inoperable cases of carcinoma of the stomach in which palliative gastro-enterostomy has been performed. The gastric acidity is also somewhat lower in gastric ulcer patients than in cases of duodenal ulcer.

An anterior gastro-enterostomy was performed in the case reported because of the large duodenal scarring, because it was technically easier and faster to do, and should a gastrojejunal ulcer occur later, it will present a much simpler surgical problem. It is believed that if gastro-enterostomy is done in any of these cases after the continuity of the gastro-intestinal tract is re-established, it should be antecolic because the occurrence of jejunal ulcer can be more readily handled. If the stomach is partially resected, an antecolic anastomosis should be done between the jejunum and stomach because gastrojejunal ulcers oc-

casionally occur after subtotal gastrectomy. Gastrojejunal ulcer following subtotal gastrectomy with a posterior anastomosis is difficult to repair.

It is preferable not to do a jejunojejunostomy since this would prevent the alkaline jejunal contents from coming into contact with the anastomotic gastrojejunal area.

Lahey believes that subtotal gastrectomy together with removal of the gastro-enterostomy and the ulcerated area at the stoma or in the jejunum is the only worthwhile method of treatment of these lesions. However, excision of the gastrojejunal ulcer and repair of the fistula with restoration of the normal gastro-intestinal continuity, if the duodenum is patent, may result in normal function, especially in the debilitated patient who cannot stand extensive gastric resection. Proper pre-operative preparation of the patient and multiple stage operations will greatly reduce the mortality and morbidity in these cases.

### ANESTHESIA

We have used a 1:1,500 dilution of nupercaine spinal anesthesia with a great deal of success. The anesthesia will last from three to three and one-half hours without very much change in blood pressure with complete relaxation of the patient. It is used in cases requiring splenectomy, subtotal gastrectomy, and where extensive colon surgery is required, and in difficult gall bladder and common duct procedures.

### PROGNOSIS

If multiple stage operations are resorted to, it is believed that the operative mortality will be considerably reduced. If one stage operations are resorted to with extensive resections, the general mortality will average in excess of 50 per cent.

After operation a great deal will depend upon the control of dietary measures and moderation in habits. Since the patient has an ulcer diathesis, he should remain indefinitely on a substantial ulcer diet and eliminate smoking and alcohol. He should also continue the use of alkalies and be periodically seen by his physician.

Walters and Clagett reported an operative mortality of 32 per cent in the fifty cases performed at the Mayo Clinic from 1928 to 1937 inclusive. Rife had a mortality of 20 per cent in fourteen cases. Lahey and Swinton (11) had an immediate mortality of 63 per cent in eight cases. Allen had a 25 per cent mortality

in eight cases. Kelly (12) advised taking down the gastro-enteric anastomosis, closing the fistula and the jejunum and then completing the operation with an extensive partial gastric resection of the Polya type all in one stage. He had an operative mortality of 25 per cent. Finsterer (13) also carried out a one-stage procedure with a mortality of 38.4 per cent.

Pfeiffer has repeatedly stressed the importance of performing a preliminary colostomy proximal to the fistula. He collected fifteen cases treated by preliminary colostomy followed by resection or restoration from members of the American Surgical Association. All of the patients were males who had had a previous gastro-enterostomy for ulcer with the single exception of a case in which spontaneous formation of the lesion occurred due to a malignant tumor of the stomach. This patient was a female. Ten of the cases were treated in the second stage by gastric resection and five by simple restoration. Fourteen recovered, one died, a mortality of only 6.6 per cent.

### SUMMARY

For some time gastro-enterostomy has been a popular therapeutic measure in the treatment of peptic ulcer. The incidence of jejunal ulcer is approximately 15 per cent and an increase in the number of cases of gastrojejuno-colic fistulas must be expected.

The great majority of jejunal ulcers follow posterior gastro-enterostomy for duodenal ulcer.

Gastrojejuno-colic fistula occurs in approximately 10 to 15 per cent of cases of gastrojejunal ulcer and in about 0.5 per cent of cases in which gastro-enterostomy is performed.

Gastrojejuno-colic fistula is a rare complication in the female sex.

The occurrence of a persistent or intermittent diarrhea in a patient who has had a gastro-enterostomy for peptic ulcer is the most outstanding symptom of fistula.

A routine surgical procedure cannot be carried out in all cases of gastrojejuno-colic fistula.

The use of multiple stage operations will greatly reduce the mortality and the morbidity. One stage procedures should not be attempted if the risk is too great. The performance of a preliminary colostomy proximal to the fistula is of utmost importance.

Since patients with gastrojejuno-colic fistulas apparently have an ulcer diathesis, a rigid ulcer regimen should be continued indefinitely after surgery.

### REFERENCES

1. Pfeiffer, O. B.: The Surgical Treatment of Gastrojejuno-colic Fistula. *S. G. O.*, 72:282-289, Feb. 15, 1941.
2. Verbrugge, Jean: Gastrojejuno-colic Fistula. *Arch. Surg.*, 11: 700-808, Nov., 1925.
3. Walters, W. and Clagett, O. T.: Gastrojejuno-colic Ulcer and Fistula. *Am. J. Surg.*, 56:94-102, Oct., 1939.
4. Rife, C. S.: Gastrojejuno-colic Fistula. *Am. J. Surg.*, 40:73-88, April, 1958.
5. Eusterman: Quoted by Walters and Clagett.
6. Allen, A. W.: An Aseptic Technique Applicable to Gastrojejuno-colic Fistula. *Surgery*, 1:338-348, March, 1937.
7. Lahey, F. H.: Diagnosis and Management of Gastrojejunal Ulcer and Gastrojejuno-colic Fistula. *Surg. Clin. N. A.*, 20:767-780, June, 1940.
8. Zweig: Quoted by Walters and Clagett.
9. Haller: Quoted by Walters and Clagett.
10. Czerny, V.: Zur Behandlung der Pissur und des Vorfalls des Mastdarms. *Beitr. z. klin. chir.*, 37:765-769, 1903.
11. Lahey, F. H. and Swinton, N. W.: Gastrojejunal Ulcer and Gastrojejuno-colic Fistula. *S. G. O.*, 61:599-612, Nov., 1935.
12. Kelly, R. E.: Recurrent Peptic Ulceration: Causes of and Design for Second Operation on Stomach. *Lancet*, 1:1-5, Jan. 7, 1939.
13. Finsterer, Hans: Results of Repeated Operations Upon the Stomach, Especially for Gastrojejunal Ulcers. *S. G. O.*, 68:234-246, Feb. 15, 1923.



## Duodeno-Colic and Gastrojejuno-Colic Fistula: A Complication of Carcinoma

### Report of Two Cases

By

MAURICE FELDMAN, M.D.\*  
BALTIMORE, MARYLAND

**F**ISTULA formation as a complication of cancer of the digestive tract is uncommonly seen, although it is not rare. Fistulous communication between the gastro-intestinal viscera is due chiefly to perforation produced either by benign ulceration or carcinoma. Perforation of the gastro-intestinal viscera caused by carcinoma, may be either acute or chronic. Acute perforation is associated with a spreading peritonitis which occurs infrequently. The more common form is the chronic type, in which there is a reaction to the peritoneum, followed by organization of exudated lymph and the production of adhesions; and in consequence the adjacent viscera become adherent and the involved area is walled off. In the latter form the process is therefore slow and sufficient time elapses to form a barrier of thickened tissue as the diseased process reaches the peritoneal coat. The walled off area thus forms a resistant wall against extension of the process. When perforation finally occurs, it is directed into the protected cavity and a chronic abscess is formed. As a rule a chronic perforation with resultant fistulous communication caused by carcinoma of the gastro-intestinal viscera, indicates an inoperable lesion. This unusual complication occurs late in the course of the disease.

The scarcity of reports on duodeno-colic and gastrojejuno-colic fistulae caused by carcinoma is not only due to the rarity of the condition, but to the fact that the hopeless outlook of cure distracts attention from this complication. Contributions on the study of duodeno-colic fistula have been made by Blondeau, Derrieu and Moramond De Laroquette, Riefenstahl and Vater and Fossati. Case reports of duodeno-colic fistula caused by carcinoma of the colon have been recorded by the following authors: namely, Segre, Ware, Mindline and Rosenheim, Burnham, Schilffarth, Gabridzhanian, Carnot and Caroli, Saleh and Hubeny and Delano. The above reports gathered from the recent available literature adds nine more cases to the total number of cases reported.

The proximity of the duodenum to the right half of colon forms an anatomic basis for the occurrence of fistulous communications between the duodenum and the colon. The second and third portions of the duodenum are the segments most frequently involved. It is interesting to note that the site of the primary carcinomatous lesion is usually in the right colon. Because of the rarity of duodenal carcinomata one would expect to find the colon as the primary seat in most cases. The colonic lesion usually found in this area, is the large fungating ulcerating carcinomata, which ulcerates through the colon into the adjacent duodenum. However, in cases of duodeno-colic fistula due

to benign ulceration the primary seat is more often in the duodenum.

Clinically the fistulous communication may not be suspected, but the occurrence of a persistent diarrhea with progressive loss of weight is very suggestive of this complication.

Fistulous communication between the small intestine and colon frequently offers considerable difficulty in diagnosis. The roentgen investigation of the bowel offers the best means of establishing a diagnosis of the primary lesion as well as the fistulous tract. Although the fistulous tract may occasionally be demonstrated by both the oral and colon enema examinations, the majority of cases will yield a demonstrable fistulous tract only after a barium enema. The condition may be entirely overlooked in the routine gastro-intestinal examination. It must be emphasized that the stream of barium flows more readily from the colon into the duodenum by way of the fistulous tract, owing to the pressure under which the enema is given and also to the propulsive peristaltic force produced by the evacuating colon. It is essential to point out that the roentgen study must be carefully planned and that painstaking care is required in order to portray the fistulous tract. An important point deserving mention, is the fact that the condition may be best demonstrated with the roentgenogram made during the expiratory phase of respiration. For further investigative purposes, in order to obtain greater clarity of the surrounding fistulous area, a relief view of the colon is of distinct advantage in educing finer details, thus giving additional information. While the complete filling of the colon with opaque media tends to obliterate and overshadow the fistulous area, it may well portray the roentgen signs of the carcinomatous lesion. On the other hand the roentgenogram made after expulsion of the barium from the colon is more apt to reveal the course of the fistulous tract, extending from the colon, and its connection with the adjacent bowel. As a further aid in the roentgen study of this condition, the insufflation of air into the colon alone, or utilizing the double contrast enema, are also helpful in demonstrating the communication between the viscera.

The following two cases, one a duodeno-colic and the other a gastrojejuno-colic fistula caused by carcinoma, are presented.

Case 1. Mrs. R. C., aged 41, entered the Sinai Hospital with the complaint of pain in the abdomen, loss of appetite, nausea and loss of weight, of four months' duration. Examination of the abdomen revealed a large firm mass in the right lower quadrant. Gastric analysis was normal. The urine was negative. Blood examination revealed a secondary anemia. Proctoscopic and cystoscopic examinations were entirely negative. Kidney studies were also

\*From the Sinai Hospital, Baltimore.  
Submitted October 10, 1941.



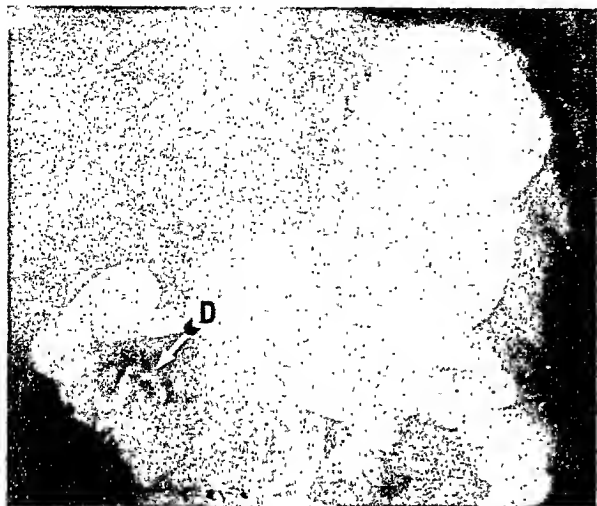


Fig. 1. Case 1. A duodeno-colic fistula. Roentgenogram revealing a duodenal diverticulum on the inner aspect of the second portion of the duodenum. Note the incomplete filling of the diverticulum, and also that it contained air.

negative. A gastro-intestinal roentgen study showed a diverticulum on the inner aspect of the second portion of the duodenum. The duodenal diverticulum was poorly filled and contained air. A barium enema depicted a filling defect at the hepatic flexure, with a large irregular pouch projecting from the inner aspect of the ascending colon. This pouch was connected at one end to the ascending colon and led toward the duodenal diverticulum in the second portion of the duodenum. It appeared that the entrance of the fistula into the duodenum was through the diverticulum. At operation the X-ray findings were confirmed. A large carcinomatous mass connecting the colon and duodenum was found.

Case 2. Mr. G. L., patient at the Sinai Hospital, complained of pains in the abdomen radiating to the left side of the back, which at first was intermittent, then became sharp and stabbing. Vomiting occurred several weeks later, and it appeared that after the vomiting began, the pains lessened and completely disappeared. Bowels were regular. There was marked weakness with progressive loss of weight. On physical examination slight tenderness was elicited in the left lower quadrant on deep pressure. The stools and urine were negative. Wassermann test was negative. There was a moderate secondary anemia. Gastric analysis revealed free hydrochloric acid, but no blood. A gastro-intestinal roentgen study was not made. A barium enema showed the stream of barium to flow from the transverse colon into the jejunum and later into the stomach, presenting the characteristic roentgen picture of a gastrojejuno-colic fistula. At operation a large carcinomatous mass was found in the left upper quadrant, involving the colon and jejunum.

#### COMMENT

The diagnosis of duodeno-colic and gastrojejuno-colic fistula due to carcinoma should, as a rule, present no difficulty following a carefully planned and painstaking roentgen study of the gastro-intestinal tract and colon. The usual evidence of carcinoma of the colon is manifested and ordinarily the disease has progressed to a late stage before this complication occurs. It must be emphasized that at times the characteristic roentgen picture of a carcinomatous lesion in the

hepatic flexure area is not always clearly discernible by the usual roentgen studies. Special effort is frequently necessary in order to depict the filling defect caused by carcinoma in the hepatic flexure region of the colon. The diagnosis of duodeno-colic and gastrojejuno-colic fistula can be definitely established by means of the X-ray examination. It is important to bear in mind that the routine gastro-intestinal study may not reveal any signs of this condition, and the complication may not even be suspected until a barium enema is made to completely examine the colon. The duodenum on account of the rapid transit of the opaque meal and the incomplete filling normally obtained in this portion of the bowel rarely yields distinct evidence of this condition. On the other hand the direct communication between the viscus may be established by administering a barium enema. In the latter examination the opaque media can be seen to flow into the fistulous tract. When the fistulous tract cannot be demonstrated, it is impossible to diagnose the true nature of the condition. The fistula varies considerably in size and length. Its lumen may be quite small, or it may be of the valve-like type. The colon at the site of the lesion will invariably yield information regarding the carcinomatous tumefaction and infiltration. Finally, the visualization of the interior of the colon following the insufflation of air is of inestimable value in clearly depicting the entire fistulous tract and its connection with the adjacent

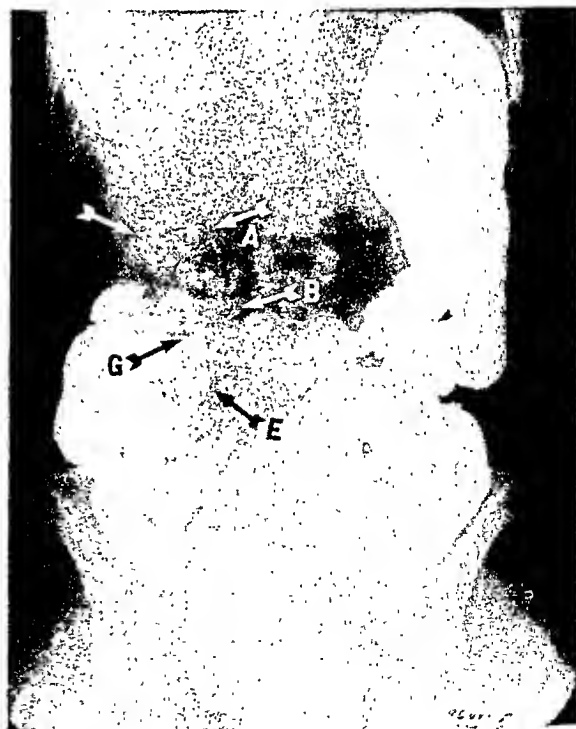


Fig. 2. Case 1. A barium enema showing the barium in the duodenum at arrow A. A fistulous tract leading into the duodenal diverticulum is shown at arrow B. At arrow E, an irregular sacular shadow is shown, coming off the inner aspect of the ascending colon. G illustrates a large annular carcinomatous defect at the hepatic flexure.

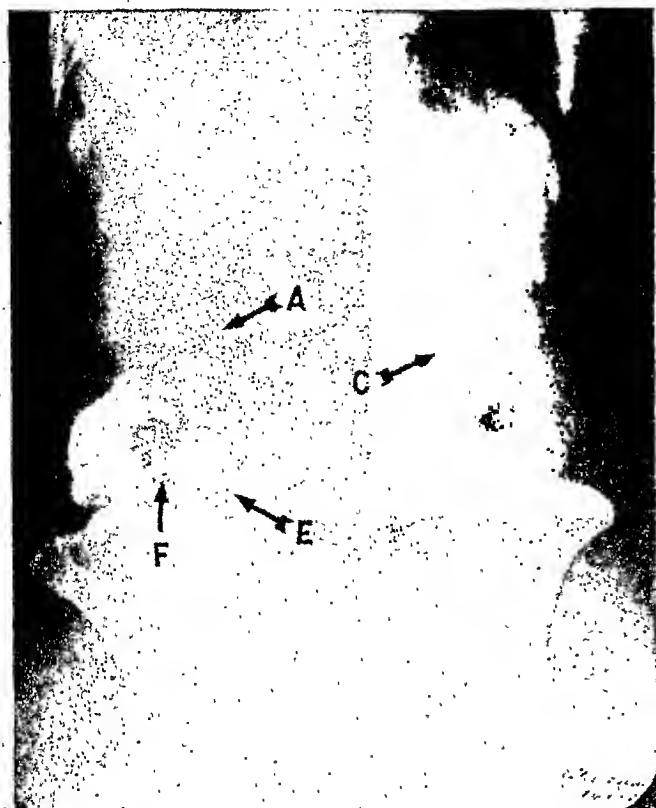


Fig. 3. Case 1. Roentgenogram following evacuation of the barium enema; note the trace of barium in the duodenum at arrow A. At arrow C, a small amount of barium is shown at the duodenojejunal flexure. At arrow E, there is an irregular pouch from which the fistulous tract enters the duodenum. At arrow F, the opening of the fistula into the ascending colon is shown.

viscera. This procedure should be utilized in the diagnosis of all doubtful cases, especially in those instances in which occlusion of the tract is suspected.

#### SUMMARY

Two cases of cancer of the colon with fistulous communication are presented, one a duodeno-colic and the other a gastrojejuno-colic fistula. This complication should be suspected if a patient with carcinoma of the bowel complains of intense pain, vomiting and diarrhea. The radiologic signs are pathognomonic in re-



Fig. 4. Case 2. A gastrojejuno-colic fistula. Roentgenogram of a barium enema after expulsion of the barium, illustrates a filling of the stomach and small intestine, in a case of carcinoma of the jejunum, demonstrating the characteristic picture of a gastrojejuno-colic fistula. Note the large irregular puddling of barium at arrows B and the fistulous opening into the stomach at arrow A. The colon is obscured by the large amount of barium in the small intestine.

vealing the lesion in the bowel as well as the fistulous tract. Of particular interest is the case of duodeno-colic fistula in which the roentgenograms revealed that the fistulous tract apparently entered the duodenum through the duodenal diverticulum. The involvement of the duodenal diverticulum in the fistulous communication is suggested by the absence of any other site of entrance into the duodenum, the fact that the diverticulum contained some air and that the fistulous tract led directly into the duodenal diverticulum.

The author wishes to express his appreciation to Dr. Alfred Ullman, Surgeon in Chief of the Sinai Hospital, for his kind cooperation in making the patients' records available.

#### REFERENCES

- Blondeau, A., Derrieu and De Laroquette, Moramond: Duodeno-colic Fistula; Roentgen Diagnosis. *Cas. Bull. et mem. Soc. de Radiol. Med. de France*, 23:433-436, 1935.
- Riefenstahl, K. and Vater, H.: Duodeno-colic Fistula; Clinical Aspects and Roentgen Diagnosis. *Röntgenpraxis*, 10:520-521, 1935.
- Fossati, F.: Contributo allo studio radiologico delle fistole colico-duodenali. *Quaderni radiol.*, 3:66-75, 1938.
- Segre, R. (Milon): Carcinoma dell'intestino con fistolizzazione ileo-colica. *Osp. maggiore*, 20:161-167, 1932.
- Ware, M.: Jejuno-colic Fistula. *Ann. Surg.*, 72:607-609, 1920.
- Mindline, J. and Rosenheim, M. L.: Duodeno-colic Fistula. Simulating Idiopathic Steatorrhea. *Lancet*, 2:764-767, 1935.
- Burnham, M. P.: Roentgen Diagnosis of Gastro-colic and Duodeno-colic Fistula. *Am. J. Roent. and Rad. Ther.*, 4:172-179, 1917.
- Schiffarth, G.: Duodenalkolonfistel bei krebs der colon ascendens. *Arch. f. Verdauungskr.*, 35:1-9, 1925.
- Gabridzhaniann, G. A.: Gastro-Intestinal Fistula in Various Parts of the Digestive Tract Caused by Cancer. *Vestnik Khir.*, 24:242-245, 1932.
- Carnot, P. and Caroli, J.: Fistule Duodeno-colique par cancer du colon. *Bull. et mem. de la Soc. med. des Hosp. de Paris*, 52:234-236, 1936.
- Salch, A. H.: Duodenocolic Fistula. *Lancet*, 2:1117, 1935.
- Hubeny, M. J. and Delmo, P. J.: Gastro-Duodeno-colic Fistula; Carcinoma of the Transverse Colon. *Am. J. Roent. and Rad. Ther.*, 43:198-200, 1940.

## Trichobezoar: Report of a Case\*

By

JEROME S. LEVY, M.D.†

and

RANDOLPH T. SMITH, M.D.‡

LITTLE ROCK, ARKANSAS

**E**ACH new case of trichobezoar or phytobezoar is of sufficient interest that it should be reported whenever encountered. Feldman (1) stated "In my experience of over 30,000 gastro-intestinal roentgen studies, no instance of this condition was observed." However, these oddities are not extremely rare as DeBakey and Ochsner (2) reviewed the world's literature up to 1939 and found 171 cases of trichobezoar had been reported since Baudamant first recorded his findings in 1779. They added one of their own and also seven additional cases of phytobezoars. Collins (3) a

### CASE REPORT

Mrs. P. H., No. 2430. Admitted to University Hospital, University of Arkansas, October 13, 1941, with the chief complaint of "Pain in stomach and mass in stomach." Duration one to two years.

Patient was not fully co-operative. She evaded questions and appeared to be mentally deficient. The history was given of a fairly sudden pain in the left upper quadrant about ten months before. It was quite severe, did not make her vomit but did make her "feel bad for a while." Since then she had had recurrent pain in the left upper quadrant, not associated with specific foods or to time of eating. At the time of the onset she discovered she was



Fig. 1. Filling defect in stomach after full barium meal. The extension into the duodenum can be seen.

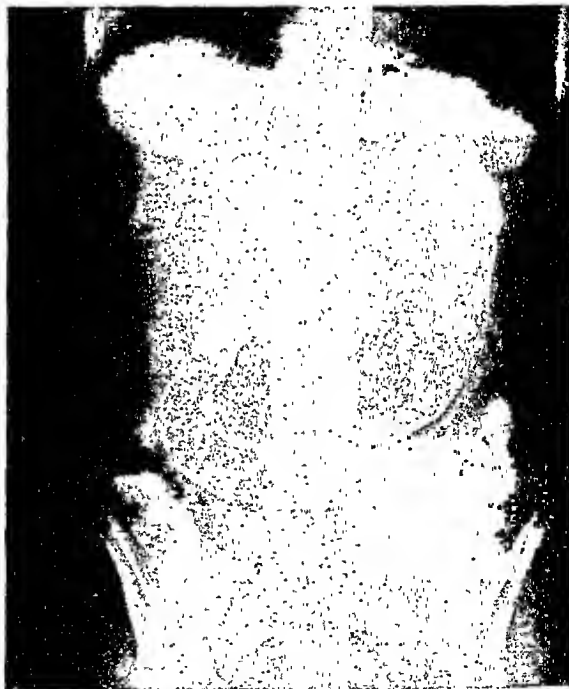


Fig. 2. Six hour film showing the barium-outlined mass in stomach, duodenum and jejunum.

few months later reported another case of trichobezoar. We have not been able to find any cases reported since his. With the present case, 174 cases will have been reported. For a thorough study of these curiosities from an historical viewpoint as well as from a complete clinical analysis, the reader is referred to the article by DeBakey and Ochsner.

\*Research Paper No. 525 Journal Series, University of Arkansas.

†Department of Medicine.

‡Department of Surgery, University of Arkansas school of Medicine.

Submitted January 1, 1942.

pregnant. After the birth of the child, which was uneventful, a mass was felt in the upper part of the abdomen. She had noted this mass for several years before, however.

On examination by one of us (J. S. L.) a mass was seen in the upper part of the abdomen extending from under the left costal margin downward toward the umbilicus and across, fading out towards the right upper quadrant. This mass seemed to be smooth, rounded, and moved on respiration. It was in the position of the stomach. On palpation it felt hard, smooth, not tender, and was of the shape of the stomach. There were no



Fig. 3. Six hour film in oblique position showing the barium-outlined mass extending from the stomach into the jejunum.

other findings on the physical examination. It was tentatively diagnosed as a bezoar and further history inquired into. It then developed that patient admitted swallowing hair and snuff during each of her three pregnancies but not at other times. The oldest child is two and one-half years old. With this additional information, a diagnosis of trichobezoar was made.

The laboratory examination showed a negative urinalysis, red blood count 4,840,000, white blood count 11,850 with a differential of 3 stabs, 70 polys, and 4 mononuclears; Hb 80%. The blood Wassermann was negative. N.P.N. 28.5 mgm. and P.S.P. 70% in two hours (40% the first half hour.) The X-ray examination showed, on a flat plate, a shadow of increased density in the region of and in the shape of the stomach. This was demonstrated by the barium meal as an intragastric mass freely movable within the stomach, and extending into the duodenum and probably also into the jejunum. (Fig. 1 to Fig. 4)

Certain features of the mental picture suggested those usually found in pellagra so patient was given thiamin chloride in 100 mgm. doses daily and nicotinic acid 100 mgm. daily for several days with a very prompt clearing up of the confused and slightly disoriented mental state.

Patient was transferred to the surgical service of Dr. R. T. Smith who did a gastrostomy on October 17, 1941. A transverse incision was made and the dark green-black mass of hair was removed. It formed a perfect east of the stomach and was covered with the usual slimy, foul, greenish-yellow fluid. The anterior surface of the fundus of the stomach about at the level of the rib margin was adherent to the anterior abdominal wall.

When the stomach had been emptied of its hair ball, a definite ulcer of the anterior wall of the stomach which had perforated and adhered to the abdominal wall was found. There was not any infiltration or exudation in the gastric wall or in the peritoneum. This possibly was the cause of the severe pain experienced at the beginning of

her last pregnancy. After the hair ball had been removed and the ulcer found and examined, it was decided to incise the duodenum and remove the remainder of the hair ball which could be felt to extend into the jejunum for an inch or two. The proximal end of the mass was fixed by an Allis forceps so as to hold it firm. As traction produced some movement more traction was employed and the entire mass was brought back through the pylorus and removed through the gastrostomy opening. The pylorus then admitted three fingers. The stomach was closed in layers and the abdominal wall likewise. Other than a short period of atelectasis of one lobe of the lung after operation, the post-operative course was uneventful and she was discharged in good physical condition on October 31, 1941.

#### COMMENT

Ulcer of the stomach or duodenum is an uncommon complication of trichobezoars and when it occurs it is usually on the lesser curvature in keeping with the usual site of gastro-duodenal ulcers. Only fifteen cases of ulcer had been found by DeBakey and Ochsner. In this case there was an ulcer on the anterior surface of the stomach high up on the fundus. Thus, sixteen cases of ulceration have been observed in 174 reported cases. Including our case, six of sixteen cases of gastro-duodenal ulceration have perforated. Adhesion to the anterior abdominal wall had prevented contamination of the peritoneum and the only symptoms had been pain extending over a period of time, localized in the left upper quadrant, following the initial sudden and fairly severe onset.

The stomach mass measured 20.0 cm. along the curved surface and 7.5 cm. by 6.0 cm. in diameter. The duodenal mass measured 27.0 cm. in total length, 6.0 cm. extending into the jejunum. The stomach mass weighed 172.0 gm. when dried, the duodenal 43.0 gm.; a total of 215 gm.

In their review, DeBakey and Ochsner did not



Fig. 4. The trichobezoar after its removal from the stomach and duodenum. The small part which extended into the jejunum has shriveled up in drying.

record any instances of extension in a continuous mass from the stomach through the duodenum into the jejunum. Mention is made of the findings of three small hair balls, each separate, in the jejunum, but none of one continuous mass. In this case the bezoar was in two main portions connected at first by a small isthmus of hair at the pylorus. This was broken deliberately to facilitate removal. The portion in the duodenum was in one piece with its continuation in the jejunum.

The mental symptoms suggested those of pellagra and cleared promptly when the patient was given nicotinic acid and thiamin chloride. The deficiency probably was the result of interference of digestion by this large mass in addition to the marginal diet which patient followed.

## CONCLUSIONS

1. 174 cases of trichobezoar have been reported in the literature. This includes the case reported in this article.

2. An additional case of gastric ulcer with perforation associated with a trichobezoar has been reported.

3. An unusual extension or prolongation of the trichobezoar into the jejunum has been recorded.

The authors wish to express their thanks to Dr. A. M. Harris, Dept. of Pathology, for the photographs of X-rays and specimen.

## REFERENCES

1. Feldman: "Clinical Roentgenology of the Digestive Tract." W. M. Wood and Co., 1932.
2. DeBakey and Ochsner: *Surgery*, 4:934-953, 1928, and 5:132-160, 1929.
3. Collins, J. D.: *Ann. of Surgery*, 102:862, 1932.

# Cellulose Splitting Micro-Organisms in Human Feces

By

NELL HIRSCHBERG, Ph.D.  
CHICAGO, ILLINOIS

ORGANISMS capable of utilizing cellulose have been isolated and studied for many years. Kellerman and McBeth (1) isolated 75 species of molds and bacteria from the soil. Later these same authors (2, 3, 4) isolated more of such organisms, attempted to classify them and discussed their metabolism. Hutchinson and Clayton (5) isolated an aerobic organism capable of decomposing cellulose. Groenewege (6) noted that certain groups of bacteria which break down cellulose contain an enzyme, cellulase. Löhnis and Lockhead (7) isolated a yellow pigmented rod capable of decomposing cellulose. Brahm (8) isolated cellulose splitting bacteria from the stomach of horses and dogs. Rege (9) showed that fungi played the most important part in the decomposition of cellulosic material, attacking the tissues after other food is used up. Bradley and Rettger (10) surveyed the literature to date and described a cellulase in cellulose decomposing bacteria which they showed to be widely distributed in nature. Winogradsky (11) discussed the disintegration of cellulose in soil. Virtanen (12) also discussed the decomposition of cellulose and the metabolism of the bacteria producing the phenomenon. Schmidt-Ott (13) stated that most organisms possess enzymes which hydrolyze cellulose and other high carbohydrates. Walker and Warren (14) tested the decomposition of cellulose by *Cytophaga* while Hooper (15) described the disintegration of the cell membrane of cotton fiber by bacteria.

The relationship of these organisms to digestion has also been studied since man ingests large quantities of cellulose in fibrous fruits and vegetables. Pringsheim (16) stated that man does not digest cellulose at all "or at most of but slight amount when in the tender forms found in certain kinds of vegetables as asparagus shoots." However, Hindhede (18) quotes Wiegner (17) and Johansson (19) to the effect that man can digest bran.

The digestion of cellulosic materials by animals has

been known for many years, McCay (20) showed that rats digested bran to the extent of 20%. Williams and Olmsted (21) noted that a certain amount of cellulose is digested when fed to humans and that the disappearance of cellulose in stools influences the volume of the feces.

Since animals are known to possess a digestive enzyme, until now not demonstrated in humans, many investigators have searched for cellulose disintegrating bacteria in the digestive tract of man. Lawrynowicz (22) isolated many such organisms from the digestive tract of animals, noting that more cellulose splitting bacteria are found in herbivorous animals. Madam Khouvine (23) isolated a strict spore bearing anaerobe apparently responsible for cellulose decomposition from the human intestinal flora which she named *E. cellulose dissolvens*.

Misra (24), Weiss and Rettger (25) and Lewis (26) investigated the bacteroides, the non-sporulating anaerobic bacteria which make up the predominance of bacteria in stools. These organisms were shown to be incapable of utilizing cellulose.

In the course of studies on the effect of bran on the human gastro-intestinal tract, it was decided to investigate the presence of cellulose splitting bacteria in human stools.

Preliminary studies indicated that fungi were the predominating cellulose splitting organisms in the human stool (27.) Attempts were made in one experiment to isolate all cellulose splitting organisms directly, utilizing the method of Aschner (29) as modified by Sullivan and Manville (28, 30.)

In a second experiment, quantitative stool counts for fungi were made and the organisms isolated were identified and tested for ability to decompose cellulose.

## PROCEDURE

Aschner's (29) method involves the use of pure cellulose membranes synthesized by strains of *Acetobacter*. This does away with the use of inorganic salts, filter paper or precipitated cellulose media.

Cultures of *Acetobacter xylinum* (No. 4939, Amer-

From the Department of Bacteriology and Public Health and the Department of Pharmacology and Therapeutics of the University of Illinois College of Medicine, Chicago, Ill.

Aided by a grant from the Kellor Company, Battle Creek, Mich.

Submitted January 1, 1942.

TABLE I

| Strain   | Number of Strains | Total Number of Strains | Number Which Utilize Cellulose |
|--|-------------------|-------------------------|--------------------------------|
| Aspergillus<br>Aspergillus fumigatus-glaucus group<br>Aspergillus with pitted stalk<br>Aspergillus niger | 32<br>1<br>12     | 45                      | 45                             |
| Hormodendrum   |                   | 22                      | 22                             |
| Oidium   |                   | 20                      | 15                             |
| Penicillium<br>1 Conidiophore<br>2 Conidiophores<br>3 Conidiophores<br>Many Conidiophores                | 1<br>3<br>1<br>9  | 14                      | 14                             |
| Endomyces  |                   | 4                       | 1                              |
| Monilia  |                   | 3                       | 3                              |
| Actinomyces  |                   | 1                       | 1                              |
| Alternaria   |                   | 1                       | 1                              |

ican Type Culture Collection) are grown on a medium consisting of 3.0% maltose, 4.0% sucrose, 0.5% powdered yeast, and 0.2% acetic acid to which 2.0% alcohol is added after sterilization. It is necessary to make frequent subcultures of the organisms at the beginning since it takes some time for them to become accustomed to the medium. They grow slowly on the surface and the culture beakers, flasks or bottles, must not be moved. Membranes of almost any desired thickness may be grown in from 6 to 14 days. Membranes are removed, treated with 5.0% sodium hydroxide for 24-48 hours, washed well in tap water and placed in dilute hydrochloric acid to remove the alkali and then washed in tap water until neutral to litmus. Before use, the membranes are partially dried and autoclaved in Petri dishes. The material to be cultured is then spread over the surface and cellulose splitting bacteria will "eat" depressions into the membrane and may be picked from the little craters for study and identification.

Samples of membranes were submitted to Dr. S. T. Gross (30), Department of Chemistry of the University of Illinois, to determine the X-ray pattern. He stated that the films are of great purity and show identical patterns with pure cellulose obtained from other investigators.

Ten per cent stool suspensions were prepared by shaking 5 gm. stool in 50 cc. of normal saline with glass beads for at least 10 minutes. Very even suspensions were obtained. One-tenth cc. of the suspension was spread over the surface of two sterile membranes in Petri dishes. One was incubated aerobically and the other anaerobically for 4 days at room temperature followed by a week at 37° C.

Organisms were picked from the depressions in the surface of the cellulose plates, sub-cultured for identification and the cellulose splitting properties checked by culture in the filter paper medium described by Walker and Warren (14.)

Very few cultures of bacteria were obtained and

most of the organisms seemed to belong to the common fungi, Aspergillus and Penicillium. It was felt that many more fungi capable of splitting cellulose were present in the stools and that the method was not very efficient for the isolation of these organisms although Aschner (29) and Sullivan and Manville (28) used this method in the quantitative investigation of cellulose splitting organisms.

For this reason a second procedure was adopted. Dilutions of stools were prepared in 100 cc. volumes of sterile normal saline solution and quantitative counts were made by the pour plate method using two different media, (a) Saboraud's agar and (b) 5% tartaric acid in 50% glucose agar. This permitted not only the isolation of fungi but a quantitative estimation of their numbers at the same time. Comparison with Aschner's method indicated the latter to be less efficient in the isolation of cellulose splitting organisms, possibly due to the necessity for the organisms to break down the membranes to obtain food for multiplication. By Aschner's method, however, a few strains of bacteria were isolated which would not grow in the acid agar plates. When checked by the filter paper method, however, these were not found to be very efficient cellulose splitting organisms.

## RESULTS

One hundred seventy-one stools from normal persons were examined. Cellulose splitting fungi were isolated from 65 of them (38%). From these 65 positive stools, 111 strains of fungi were isolated and identified. Table I shows the results.

The predominance of members of the Aspergillus group is obvious and, as expected, due to its wide distribution.

The most interesting result is that of the isolation of 20 strains of Oidium, 15 of which were able to grow on filter paper, thus indicating ability to utilize cellulose as food and 5 strains of which showed no such property. Further study and possible separation into species is now in progress.

Sixty-eight stools from constipated persons were examined. Cellulose splitting fungi were isolated from 24 of them (35%). From these 24 positive stools, 52 strains of fungi were isolated and identified. Table II shows the results.

TABLE II

| Strain  | Number of Strains | Total Number of Strains | Number Which Utilize Cellulose |
|---|-------------------|-------------------------|--------------------------------|
| Aspergillus<br>Aspergillus fumigatus-glaucus group<br>Aspergillus niger | 16<br>10          | 26                      | 26                             |
| Penicillium<br>1 Conidiophore<br>2 Conidiophores<br>Many Conidiophores  | 1<br>2<br>5       | 8                       | 8                              |
| Hormodendrum  |                   | 6                       | 6                              |
| Oidium  |                   | 5                       | 5                              |
| Alternaria  |                   | 3                       | 3                              |
| Actinomyces   |                   | 1                       | 0                              |



Several strains of bacteria were isolated from the stools by the cellulose plate method. These organisms could not utilize filter paper. Their cellulose splitting properties are being further studied. Most of them were strains of *Aerobacter*.

### COMMENT

From these findings it will be seen that many human stools contain large numbers of fungi capable of decomposing cellulose. Since it is known that man can digest a certain amount of cellulose, and since man possesses no known enzyme capable of assisting in the digestion of cellulose, it is possible that these micro-organisms may play an important role in the human use of cellulosic foods.

Cellulose splitting fungi were isolated from approxi-

mately the same percentage of stools of constipated persons as from normal stools. It seems possible that constipated persons utilize approximately the same amount of cellulosic food as normal persons. Any additional cellulosic food may remain unchanged and thus probably add to the bulk of the stool.

### SUMMARY

One hundred seventy-one stools from normal persons were examined for the presence of cellulose digesting micro-organisms. 111 strains of common fungi were isolated from 65 (38%) of these stools.

Sixty-eight stools from constipated persons were examined for the presence of cellulose digesting micro-organisms. 52 strains of common fungi were isolated from 24 (35%) of these stools.

### REFERENCES

1. Kellerman, K. F. and McBeth, J. G.: Soil Organisms Which Destroy Cellulose. *Centr. Bakt.*, 34:63, Abt. 2, 1912.
2. Kellerman, K. F. and McBeth, J. G.: The Fermentation of Cellulose. *Centr. Bakt.*, 34:485, Abt. 2, 1912.
3. McBeth, J. G., Scales, F. M. and Smith, W. R.: Characteristics of Cellulose-Destroying Bacteria. *Science*, 38:415, 1913.
4. McBeth, J. G. and Scales, F. M.: The Destruction of Cellulose by Bacteria and Filamentous Fungi. U.S.D.A., Bur. Plant Ind. Bull. No. 266, 1913.
5. Hutchinson, H. and Clayton, I.: On the Decomposition of Cellulose by an Aerobic Organism. *J. Agric. Sci.*, 9:743, 1919.
6. Groenewege, J.: Untersuchungen über die Zersetzung der Zellulose durch Aerobe Bacterien. *Abstr. Cent. Bakt.*, 53:414, Part 2, 1921. (*Orig. Bull. du Jardin. Botan. de Buitenzorg.*, Ser. 4, T. 2, Fasc. 3, p. 261, 1920.)
7. Lohnis, F. and Lockhead, G.: Experiments on the Decomposition of Cellulose by Aerobic Bacteria. *Cent. Bakt.*, 58:430, Abt. 2, 1922.
8. Brahm, C.: Determination of Digestibility of Cellulose Fodder with Bacteria from Stomach of Ruminants. *Biochem. Zeit.*, 175:28, 1926.
9. Rege, R. D.: Bio-Chemical Decomposition of Cellulosic Materials, with Special Reference to the Action of Fungi. *Ann. Appl. Biol.*, 14:1, 1927.
10. Bradley, L. A. and Rettger, L. F.: Studies on Aerobic Bacteria Commonly Concerned in Decomposition of Cellulose. *J. Bact.*, 13:321, 1927.
11. Winogradsky, S.: Sur la Degradation de la Cellulose dans le Sol. *Ann. Inst. Pasteur*, 43:549, 1929.
12. Virtanen, A. L.: On the Enzymes of Bacteria and Bacterial Metabolism. *J. Bact.*, 28:447, 1934.
13. Schmidt-Ott, A.: Studien über Zelluloseverdauung. *Arch. f. Verdauungstr.*, 69:143, 1936.
14. Walker, E. and Warren, F. L.: Decomposition of Cellulose by Cytophagy. *J. Biochem. J.*, 32:31, 1938.
15. Hooper, F. E.: Disintegration of the Cell Membrane of the Cotton Fiber by a Pure Culture of Bacteria. *Contr. Boyce Thompson Inst.*, 10 (3), 267, 1939.
16. Pringsheim: Chemistry of the Saccharides. New York, 1932.
17. Wiegner: Mitt. d. Gesellsch. Schweizerisch. Landwirte, No. 5, 1918.
18. Hindhede, M.: Protein and Pellagra. *J. A. M. A.*, 80:1635, 1923.
19. Johansson: *Svenska Lak. Sallsk. Forhandl.*, p. 302, 1917.
20. McCay, C. M.: Cellulose in the Diet of Rats and Mice. *J. Nutrit.*, 8:435, 1934.
21. Williams, R. D. and Olmsted, W. H.: The Manner in Which Food Controls the Bulk of the Feces. *Ann. Int. Med.*, 10:717, 1936.
22. Lawrynowicz, A.: Presence de Microbes Aerobes Decomposant la Cellulose dans le Tube Digestif. *C. R. S. de Biol.*, 122:839, 1936.
- 23a. Khourine, Y.: Digestion de la Cellulose par la Flora Intestinale de l'Homme. *Ann. de l'Inst. Past.*, 37:711, 1923.
- 23b. Khourine, Y.: Cellulose et Bacteries, Decomposition et Synthese. Paris, 1934.
24. Misra, S. S.: A Note on the Predominance of the Genus Bacteriodes in Human Stools. *J. Path. and Bact.*, 46:204, 1938.
25. Weiss, J. E. and Rettger, L. F.: The Gram Negative Bacteriodes of the Intestine. *J. Bact.*, 33:423, 1937.
26. Lewis, K. H.: Non-Sporulating Anaerobic Bacteria of Intestinal Origin. *Thesis*, Yale University, 1939.
27. Hirschberg, N.: Cellulose Splitting Bacteria Isolated from Human Stools. *Abst. J. Bact.*, Vol. 41, 78, 1941.
28. Sullivan, N. P. and Blauville, I. A.: The Relationship of the Diet to the Self-Regulatory Defense Mechanism. I. Hydrogen-ion Concentration and Bacterial Flora. *Am. J. Dig. Dis.*, 5:428-432, Sept., 1939.
29. Aschner, M.: Cultivation of Cellulose-Splitting Bacteria on Membranes of *Aerobacter xylinum*. *J. Bact.*, 33:249, 1937.
30. Sullivan, N. P.: Personal communication.
- Gross, S. T.: Personal communication.

## The Influence of Certain Commonly Used Drugs on the Rate of Gastric Emptying in the Normal Human Subject as Determined by an Intubation Technique

(Atropine, Morphine, Benzedrine, Prostigmine, Nitroglycerine, Syntropan, Mecholyl, Ergotamine Tartrate and Sodium Bicarbonate)

By

JARRETT H. FOLLEY, M.D.

and

W. OSLER ABBOTT, M.D.

PHILADELPHIA, PENNSYLVANIA

**T**O restudy the normal human gastric emptying time in the face of all the published data on the subject seems very much like beating a dead dog. Nevertheless one phase of the problem remains for quantitative appraisal, and that is the rate at which the main bulk of the contents is evacuated as distinct from the total emptying time. Most of the reported studies have been conducted by the roentgenological technique, which

gives in exact figures only the beginning and the end of the period. Since the stomach meanwhile is secreting at a variable rate and since some saliva normally is swallowed, the time of disappearance of the last fleck of an opaque meal may bear little relationship to the rate at which the first ninety per cent of the initial volume leaves. Although a shrewd fluoroscopist can make an estimate of the percentage leaving the stomach at short intervals, we have attempted to quantitate this phase of gastric emptying both after the administration and in the absence of

From the Gastro-Intestinal Section, (Kinsey-Thomas Foundation) of the Medical Clinic, Hospital of the University of Pennsylvania.  
Aided by a grant from the Smith, Kline & French Laboratories.  
Submitted Jan. 2, 1942.

certain common drugs that are supposed to have the power to influence the process.

### METHOD

The requirements of this quantitative study of the rate of gastric emptying were (a) that it be done on normal subjects, (b) that it be clinically practical, (c) that it not disturb approximately normal physiologic conditions and (d) that it yield ample and exact data.

Five normal adult subjects, as determined by history, physical examination, gastric analysis and gastro-intestinal roentgenoscopy, were chosen. An effort was made to select only emotionally stable individuals who could be used repeatedly over a long period. On the day of the experiment these subjects ate a normal breakfast and thereafter took water as they desired until the time of the noon meal when the test was carried out.

A soft rubber gastric tube, 6 mm. in diameter, was then passed into the stomach, the subject being placed prone on a couch with her head to the left and being instructed to expectorate all saliva into an emesis basin placed by her cheek. When the subject was comfortable, the tube was attached to a 500 cc. graduated cylinder, arranged in series with a syphon suction system. A solution could thus be caused to flow rapidly from the stomach to the graduate or back again.

The test solution was a 1 to 20 dilution of evaporated milk\* in water at room temperature. This represented a common-place food containing protein, fat, carbohydrate and salt, but one that, because of its fine curd, flowed freely. After a preliminary introduction and removal of 300 cc. of tap water, to wash out the mucus or saliva, 500 cc. of the milk mixture were placed in the graduate and caused to flow into the stomach.

At ten minute intervals thereafter suction was applied, the gastric residue drawn into the flask, its volume measured and the whole returned again to the stomach. Never more than five minutes were consumed in the withdrawal and re-introduction. Often much less than five minutes was consumed, but if a sharp diminution in volume occurred the tube was moved in the stomach to assure complete emptying. This time has not been charted and the ten minute interval was taken from the completion of filling to the beginning of emptying. This procedure yielded data for a five to ten point curve on the average. The experiment was stopped when the volume had been reduced to approximately 50 cc.

The drugs employed were given either subcutaneously or by mouth. The gastric filling was begun one to two minutes following a subcutaneous injection. When the oral route was used the drug was given in

\*Pet.

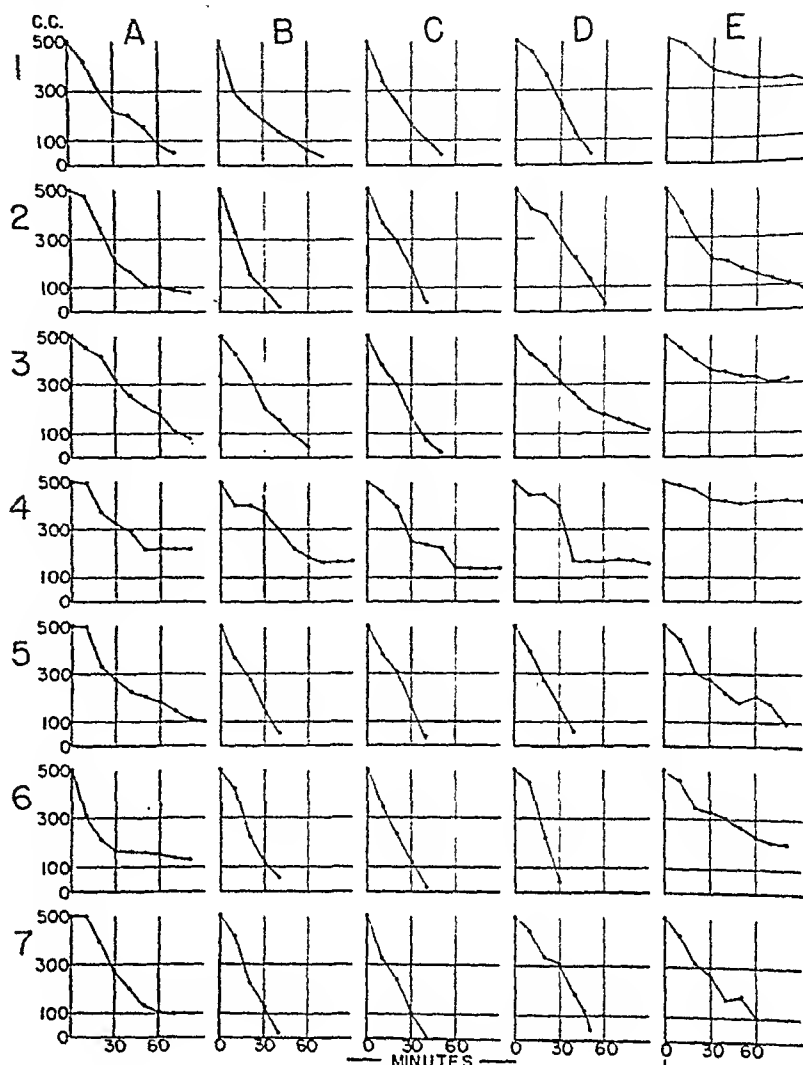


Fig. 1A. The results of 70 experiments on the rate of gastric emptying of 5 normal adults with and without medication. Columns A, B, C, D and E represent the responses of the five individuals respectively. Rows 1 to 7 represent the different experimental procedures applied in identical fashion to each of the five subjects, viz.: No. 1—No drug given; No. 2—Atropine sulphate, 0.4 mgm. (gr. 1/150) subcutaneously; No. 3—Atropine sulphate, 0.8 mgm. (gr. 1/75) subcutaneously; No. 4—Morphine sulphate, 10 mgm. (gr. 1/6) subcutaneously; No. 5—Amphetamine sulphate (Benzedrine) 10 mgm. (gr. 1/6) subcutaneously; No. 6—Atropine sulphate, 0.8 mgm. (gr. 1/75) by mouth; No. 7—Prostigmine, 0.5 mgm. (gr. 1/120) subcutaneously.

60 cc. of water following the initial lavage. Gastric filling was begun 30 minutes later.

### RESULTS

The complete data from 70 experiments are shown in Fig. 1a and b. The similarities in the curves are far more striking than the differences. One cannot distinguish the results of the control experiments from those involving the administration of a drug with certainty save in the case of morphine which in each instance showed a delayed inhibition of gastric emptying. In general there was more similarity in the response of the same patient given different drugs than in the response of different patients to the same drug. It is probably significant that "C" who has served as a paid subject with great regularity for over 4 years showed the most uniform response irrespective of the drug given (Fig. 2), while "E," who

first joined us at the start of these observations and who never has succeeded in facing a stomach tube with the complete equanimity which we desire, showed the greatest irregularity.

The following drugs were given: atropine sulphate, 0.4 and 0.8 mgm. (gr. 1/150 and 1/75) subcutaneously and 0.8 mgm. (gr. 1/75) by mouth; morphine sulphate, 10 mgm. (gr. 1/6) subcutaneously; amphetamine sulphate (Benzedrine), 10 mgm. (gr. 1/6) subcutaneously; prostigmine, 0.5 mgm. (gr. 1/120) subcutaneously; nitroglycerine, 0.6 mgm. (gr. 1/100) by mouth; "Syntropan," 90 mgm. (gr. 1½) by mouth; acetyl-B-methylcholine chloride (Mecholyl), 5 or 10 mgm. (gr. 1/12 and 1/6) hypodermically; ergotamine tartrate (Gynergen), 0.25 mgm. (gr. 1/240) subcutaneously; and sodium bicarbonate, 1 gm. (gr. 15) by mouth. Each produced side effects when expected. Subject D received 10 mgm. of Mecholyl but was so disturbed by the cardiovascular reactions that in the remaining 4 subjects 5 mgm. was used at the risk of its being an ineffective dose. Sweating and tachycardia resulted none the less.

### DISCUSSION

The determination of the gastric emptying curve being the subject of this study, its physiologic significance must be defined. Basically the emptying rate is a measure of the movement of a liquid through a tube of varying physical character and is therefore the resultant of several forces, i.e. the propulsive pressure of the gastric contractions, the resistance offered by the intra-intestinal pressure when the pylorus is open or by a localized contraction at the pylorus or duodenum when such a response closes the lumen. To these must be added the controllable factor of the viscosity of the contents. One must further consider that the propulsive force may probably be developed by the stomach either through a generalized tonic contraction of the whole organ or locally through the action of antral peristalsis. It becomes plain, then, that the gastric emptying curve is the sum total of the responses of the upper end of the alimentary canal, as defecation is the sum total of responses at the lower end. Nevertheless, if we are to attempt an analysis of the mechanism by which common drugs affect the digestive system, this general effect must be known before the particular factors are considered.

The method used has proved technically satisfactory. Quantitative results are obtainable with an accuracy not matched by roentgenography. Emptying can be completed within a probable error of 5 cc. without expending undue time. When emptying has not been complete, the volume is excessive on the next collection and the error is at once apparent on the graph (Fig. 1a-E-7.) This of course is not the only explanation of such an irregularity in the curve, however. Duodenal regurgitation and gastric secretion may augment the

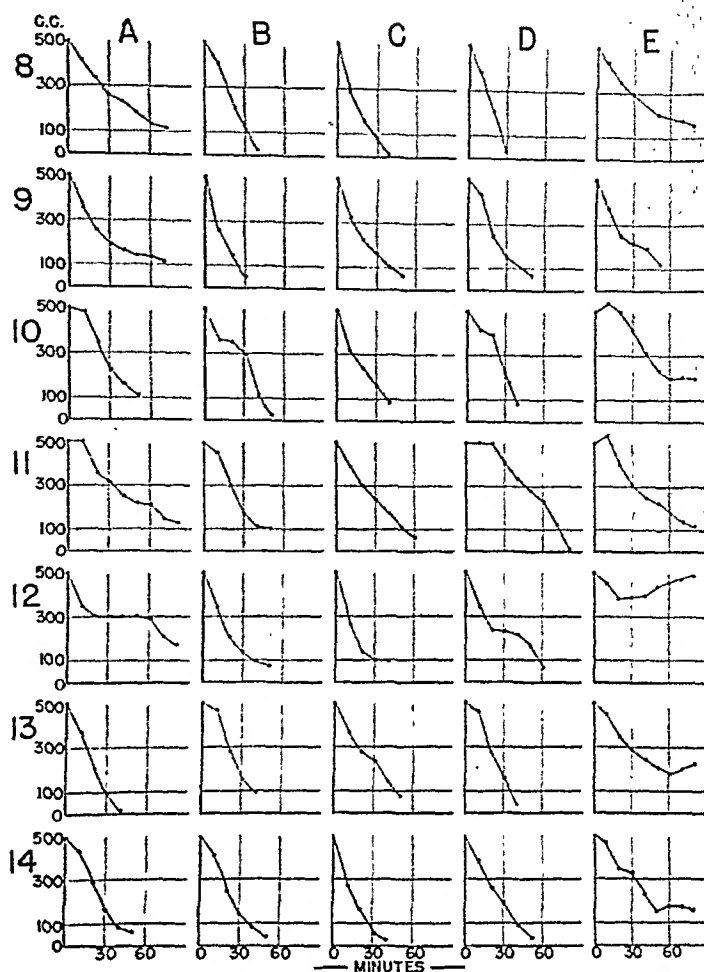


Fig. 1B. The results of 70 experiments on the rate of gastric emptying of 5 normal adults with and without medication. Columns A, B, C, D and E represent the responses of the five individuals respectively. Rows 8 to 14 represent the different experimental procedures applied in identical fashion to each of the five subjects, viz.: No. 8—Physiological salt solution, 0.5 cc. subcutaneously; No. 9—Nitroglycerine, 0.6 mgm. (gr. 1/100) by mouth; No. 10—"Syntropan," 90 mgm. (gr. 1½) by mouth; No. 11—Acetyl-B-methylcholine chloride (Mecholyl), 5 mgm. (gr. 1/12) subcutaneously; No. 12—Ergotamine tartrate (Gynergen), 0.25 mgm. (gr. 1/240) subcutaneously; No. 13—Sodium bicarbonate, 1 gm. (gr. 15) by mouth; No. 14—No drug given.

gastric volume. Close watch convinces us that the swallowing of saliva has not significantly influenced the volume. The omission of the time lost in filling and emptying the stomach from our consideration is justified by the fact that practically all the contents can be removed in 90 seconds and if two or three more minutes are needed in removing the last 5 or 10 cc. it is probably of small consequence.

Morphine, alone, produced a characteristic curve in each instance. Its shape is compatible with the changes in gastro-intestinal activity described as characteristic of the drug by Abbott and Pendergrass (1). Since in that study other factors of drug action were under consideration this is a circumstantial rather than a direct confirmation. It is of great importance in this study, however, for without one sharply differentiated reaction for comparison the similarity of all other curves would be less evident.

There is little that can be said about the actions of the other drugs used. One may suggest that it is easier to delay than to accelerate emptying and that any drug reaction severe enough to upset a subject may do this. If other actions resulted from these drugs they were not such as to alter the gastric emptying time. With greater variation in the dosage or route of administration this might have been altered but amounts were used capable of producing the characteristic side effects we were expecting. Possibly atropine (Fig. 1a, C2, 3 and 6) lowered the intra-gastric and

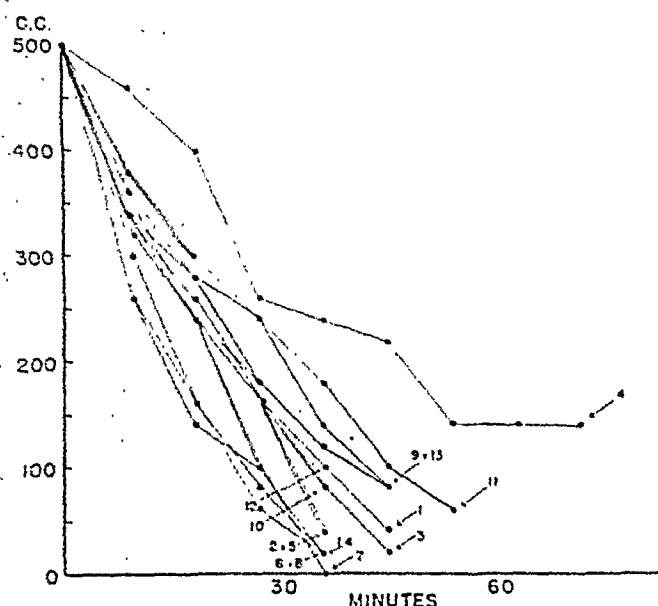


Fig. 2. The results of experiments shown in Fig. 1 on subject "C" are here superimposed for comparison.

intra-duodenal pressure and physostigmine (Fig. 1a, C7) raised them in exact proportion, accounting for identical emptying rates, but it is noteworthy that these four curves all fall between the controls (Fig. 1a, C1) and (Fig. 1b, C8 and 14.) We believe from a great mass of experimental data in the literature that these drugs are not without effect on the digestive tract, and it is quite possible that many changes in behavior took place in our subjects, but if such was the case the algebraic sum of those diverse actions, that is to say, the rate of gastric emptying, remained essentially constant.

Finally, it must be stated that what is true of the normal stomach may not be true of the diseased or disordered viscus. There is ample evidence to suggest that the contracted stomach and the relaxed stomach respond differently to the same stimulus and until this work is repeated on patients with symptoms the question must remain open.

### CONCLUSIONS

The gastric emptying curve of five normal human subjects as obtained by repeated aspiration, measurement and reinjection of a test solution was essentially unaltered by clinical doses of atropine sulphate, amphetamine sulphate, prostigmine, nitroglycerine, "Syntropan," acetyl-B-methylcholine chloride, ergotamine tartrate or sodium bicarbonate.

Morphine sulphate produced a delayed inhibition of gastric emptying in each of five experiments.

### BIBLIOGRAPHY

1. Abbott, W. O. and Pendergrass, E. P.: Intubation Studies of the Human Small Intestine; V. The Motor Effects of Single Clinical Doses of Morphine Sulphate in Normal Subjects. *Am. J. Roent.*, 35:289-299, March, 1936.

## Some Factors Concerned in the Production of Experimental Ulceration of the G-I Tract in Cats\*

By

M. J. SCHIFFRIN, Ph.D.†

and

ALTHEA A. WARREN, M.A.

MONTREAL, CANADA

IT is generally agreed that the action of gastric juice is one of the important factors in the etiology of peptic ulcer. In recent years the role of the acidity of the gastric juice has been emphasized almost to the exclusion of that of the pepsin in the juice, especially by Dragstedt (1917), Dragstedt and Matthews (1933), McCann (1929), and Mann and Bollman (1932.) There are, however, at least two considerations which make this concept questionable. First, few experiments have been performed that would adequately distinguish the effects of acid from those of pepsin in an acid medium. Second, ulceration of the gastro-intestinal tract has never been produced by physiological concentrations of acid in the absence of pepsin. In view of these con-

siderations it was decided to test the validity of the concept of "acid ulcer" by more adequate methods. A procedure based on the methods of Matthes (1893) and Langenskiöld (1913) has been devised (Schiffirin, 1940) which allows for the perfusion of segments of the gastro-intestinal tract *in situ* with solutions of acid or with pepsin in an acid medium in acute experiments on cats. In preliminary experiments it was found that acid *per se* had little effect on the jejunal mucosa, but a solution of pepsin in acid produced ulceration within 12 hours of time. The present communication describes the application of this method to the stomach, duodenum and ileum. The threshold of peptic activity necessary for ulceration of the jejunal mucosa, and the effect of pH thereon has been determined. The principles of the acute method have also been applied in chronic experiments.

\*From the Department of Physiology, McGill University, Montreal.  
†At present at the Department of Physiology, Northwestern University, Chicago, Illinois.  
Submitted Dec. 1, 1941.

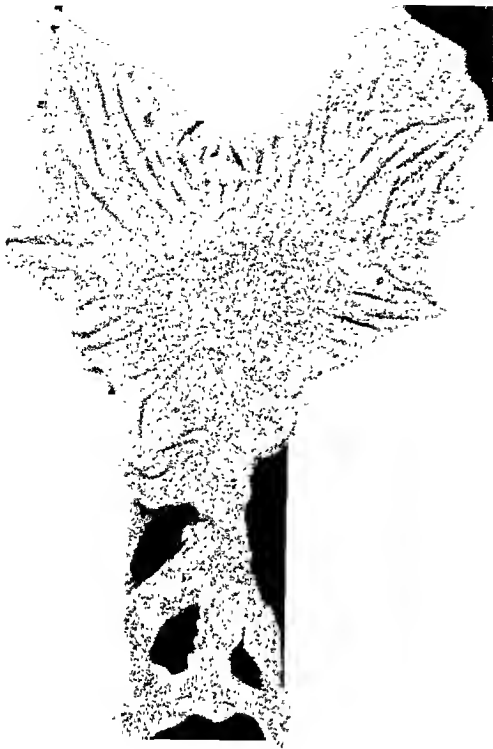


Fig. 1. Stomach and duodenum after 12 hours' perfusion with 3 per cent 1:3,000 pepsin in HCl (pH 1.2.)

In addition to comparing the ulcerative action of acid and acid-pepsin, the relative resistance of the various parts of the gastro-intestinal tract to the action of these substances has been studied. This was done in order to determine if a gradient of the susceptibility of the mucosa exists from the pylorus to the ileocecal sphincter. This problem is of practical interest to the surgeon when he makes an anastomosis between the stomach and some part of the bowel. A preliminary report of this work has appeared (Schiffman and Warren, 1941.)

#### EXPERIMENTAL

**Acute experiments: Methods.** All the experiments were performed on cats under Nembutal anesthesia. The portion of the gastro-intestinal tract to be studied was cannulated both orally and distally, care being taken to avoid any circulatory damage. The segment was replaced in the abdominal cavity and the open ends of the cannulae were brought through stab incisions in the abdominal wall. The solution to be perfused through the segment was introduced via the distal cannula and drained proximally. The rate of flow was 1-2 cc. per minute and all the solutions were brought to body temperature before perfusion. After 12 hours of perfusion the segments were removed, examined grossly, and then fixed for histological study.

The free and total acidities of the perfusing fluid were determined by titration with 0.02 N NaOH, Töpfer's reagent and phenolphthalein being used respectively as indicators. Pepsin was determined by Nirenstein and Schiff's modification of Mett's method. The Beckman glass electrode potentiometer was used

for the determination of pH. The pepsin used in this study was either 1:3,000 (Parke, Davis & Co.) or 1:10,000 (John Wyeth & Bro., Inc.)

**Effects of acid, pepsin and acid, and gastric juice.** Sixteen experiments were performed in which a loop of jejunum was perfused for 12 hours with hydrochloric acid, pH 1.2-1.3 (approximately N/10.) No bleeding, ulceration, or perforation of the loop occurred during any of these experiments. The mucosa presented a greyish, necrosed appearance, but histological examination revealed little damage of the villi.

In 53 experiments the jejunum was perfused with a 3 per cent solution of 1:3,000 pepsin in approximately N/10 HCl. The pH of this solution was the same as that of the acid used in the previous series, namely, 1.2-1.3. Ulceration, sometimes leading to perforation, developed in all of these experiments. In all but 2 cases bleeding occurred. Similarly, pepsin in an acid medium was more effective than acid alone in producing damage to the duodenum and ileum. The difference between the action of acid alone and pepsin with acid was not so marked on the gastric mucosa. This was probably due to the presence of pepsin in the stomach during the perfusion with acid, for analysis of the acid after it had passed through the stomach showed that it had acquired some peptic activity. Fig. 1 shows the appearance of the stomach and duodenum after being perfused for 12 hours with 3 per cent 1:3,000 pepsin in HCl (pH 1.2.) In this particular experiment there were many small ulcers along the lesser curvature of the stomach, and the duodenum was perforated in three places.

Two experiments were performed in which the jejunum was perfused with canine gastric juice. Ulceration developed in both instances. In the first experiment the peptic power of the juice was 58 Mett units; in the second, 92 Mett units. The pH was 1.32 and 1.08, respectively.

**Threshold of peptic activity.** The concentration of pepsin was varied, while the pH was kept constant in a series of 30 experiments. The minimum concentration of pepsin necessary to produce ulceration of the jejunum under these experimental conditions was 0.1-0.2 per cent 1:10,000 pepsin at pH 1.2-1.3. This concentration is equivalent to 58-100 Mett units. These values are comparable with those of gastric juice obtained during the chemical phase of canine gastric secretion. This study brought other considerations to our attention. There had not been much difference in the susceptibility of the mucosa of the animals in the earlier experiments when high concentrations of pepsin were used. However, when threshold concentrations were employed, the degree of ulceration was not the same among all the animals. This may be due to some systematic or inherent differences in the resistance of the tissue of different animals to digestion, which being relatively small, could be observed only when small concentrations of pepsin were employed.

**Effect of pH.** In order to determine the effect of pH, this factor was varied and the concentration of pepsin was kept constant. The different pH levels were obtained by using various amounts of hydrochloric acid and distilled water. Introduction of a buffer was avoided because it was feared that this might affect the peptic activity of the solution. The results of some of the experiments are shown in Table I. When

the pH of the solution was 2.24, there was no digestion, although the amount of pepsin used was greater than in the other experiments. These data indicate that the optimum pH for ulceration of the jejunum under these experimental conditions was 1.1-1.5. This pH is within the optimum range for peptic digestion.

*Relative resistance of the stomach, duodenum, jejunum and ileum.* It has been indicated that acid caused some damage to the gastric mucosa and that this may have been due in part to the action of pepsin

TABLE I

*The effect of pH on peptic digestion of the jejunum*

| Date     | Hours of Perfusion | Peptic Power Mett Units | pH   | Degree of Digestion† |
|----------|--------------------|-------------------------|------|----------------------|
| 1-6-41   | 12                 | 90                      | 2.24 | 0                    |
| 12-11-40 | 11                 | 58                      | 2.18 | x                    |
| 12-20-40 | 12                 | 58                      | 2.00 | x                    |
| 12-9-40  | 11½                | 58                      | 1.75 | xx                   |
| 12-11-40 | 11                 | 58                      | 1.75 | xx                   |
| 12-11-40 | 11                 | 58                      | 1.55 | xxx                  |
| 12-13-40 | 12                 | 58                      | 1.50 | xx                   |
| 12-13-40 | 12                 | 58                      | 1.10 | xxxx                 |
| 12-18-40 | 6½                 | 58                      | 1.15 | xxx                  |

†The degree of digestion of the intestine is expressed as follows: 0, normal mucosa; x, minor damage to the villi and some necrosis; xx, bleeding, with not more than two areas of ulceration; xxx, bleeding, with more than two areas of ulceration; xxxx, bleeding, with profuse ulceration and perforation.

normally present in the stomach. However, acid caused more damage to the duodenum than to either the jejunum or ileum in the absence of pepsin. In those experiments in which the duodenum was perfused with acid, both the pancreatic and biliary ducts were ligated to prevent neutralization. No experimental evidence was obtained which would satisfactorily explain the susceptibility of the duodenum to the action of acid. There was no apparent difference between the action of acid on the jejunum and on the ileum for ulceration did not occur. The addition of pepsin to the acid increased the degree of ulceration in all parts of the gastro-intestinal tract.

*Chronic experiments: Methods.* Seven cats were equipped with gastric fistulae under aseptic conditions. Spool-shaped cannulae were cut from one-hole rubber stoppers. Each cannula was fitted with a tight-fitting glass stopper that could be removed at will. After the animals had recovered from the operation they were subjected to the following procedure. At the start of experimentation, 30 cc. of either acid alone or pepsin in acid were introduced into the stomach via the fistula with the aid of a syringe and soft rubber catheter. One hour later, the contents of the stomach were removed, and both the acidity and the peptic activity of the contents determined. Another 30 cc. of acid or pepsin in acid were again placed in the stomach. This was continued for 8 hours each day. On completion of the day's experiment, disodium citrate (Parke, Davis & Co.'s "Liquid Citralka") was administered through the fistula in sufficient quantity to neutralize the calculated absorbed acid. A weighed portion of food was then presented to the animal. Any food remaining 5 hours later was removed in order to

make certain that the stomach of the animal was empty at the start of the next day's experimentation. A record was kept of the animal's weight and the amount of food consumed each day.

*Results with acid alone.* Cat No. 5 was treated with approximately N/10 HCl (pH-1.2.) The animal died after 18 days with no disease of the gastro-intestinal tract. It is possible that acidosis was the cause of death because the animal was often unable to retain the disodium citrate at the end of the experimental day. The pH of the urine was 3.5 a few days before death. The lowest urinary pH observed in any of the other animals was 5.0.

Cat No. 6 was sacrificed after 8 days' administration of acid and there were no pathological changes in the gastro-intestinal tract. Cat No. 7 was also sacrificed after 8 days and a small, indurated ulcer was found in the cardia of the stomach. There were no other pathological changes in the gastro-intestinal tract. It is interesting to note that the peptic power of the gastric contents was greater in cat No. 7 than in the others treated with acid, values as high as 100 Mett units being often observed in this animal.

*Results with pepsin in acid.* The solution used in this series was 3 per cent 1:3,000 pepsin in HCl (pH 1.2-1.3.) Cat No. 1 died of a perforated gastric ulcer after 5 days of this treatment. The appearance of the stomach at autopsy is shown in Fig. 2. The perforation, which was about 1 cm. in diameter, occurred in the region of the lesser curvature and the incisura angularis. There were in addition many areas of ulceration in the fundus of the stomach. A section of the edge of the perforated ulcer was fixed for histological examination. This is shown in Fig. 3. Dr. T. R. Waugh, of the Pathological Institute of McGill University, examined this section and reported that it



Fig. 2. Stomach after 5 days during which pepsin and acid were introduced daily.

displayed most of the characteristics of human peptic ulcer.

Cat No. 2 died of hemorrhage after 8 days' treatment with acid and pepsin. The picture of the stomach at autopsy is shown in Fig. 4. The wound through which the fistula was introduced is on the left side of the picture and it may be seen that the tissue adjacent to it was not damaged. The areas of ulceration and necrosis appear as dark portions in the picture. The deepest ulcer was in the same position as the perfo-



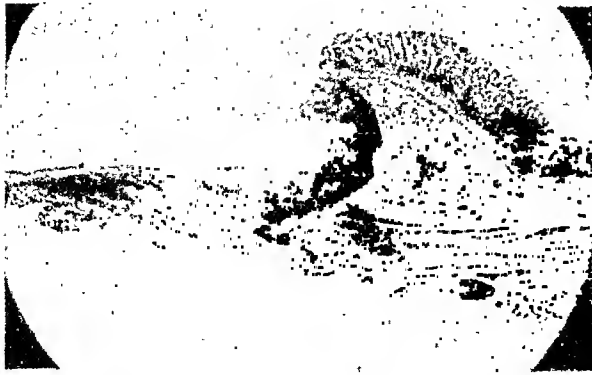


Fig. 3. Histological section of perforated ulcer shown in Fig. 2.

ration in cat No. 1, namely, at the junction of the lesser curvature and the incisura angularis.

Cat No. 3 died of hemorrhage after 7 days' treatment with acid and pepsin. The appearance of the stomach at autopsy was similar to that of cat No. 2. All 3 of these animals exhibited the following symptoms as ulceration developed. Vomiting occurred after the first day's experimentation and daily became more frequent and severe. The volume of fluid retained in the stomach during the experimental period increased and the neutralization of the acid decreased. There was no sign of any pathological changes in the duodenum or jejunum in any of these animals at autopsy.

Cat No. 4 differed from the other animals treated with acid and pepsin. Vomiting and retention of fluid in the stomach did not appear until after 2 weeks of experimentation. The only damage found when the animal was sacrificed after 25 days was a small ulcer in the duodenum just distal to the pylorus.

#### DISCUSSION

The acute experiments were similar to those performed by Langenskiöld (1913.) The uncertainty of some of his results may be ascribed to the fact that none of his experiments were of more than 4 hours' duration, whereas our experiments were usually continued for 12 hours. Our observations on the resistance of the various parts of the gastro-intestinal tract to acid are not in agreement with those of other investigators, who reported the upper regions of the tract to be most resistant. The damaging effect of acid on the gastric mucosa may perhaps be due in part to the pepsin normally present in the stomach. However, there is no obvious reason why the duodenum should be so susceptible to acid. Under normal conditions the duodenum is protected by the secretion of alkaline pancreatic juice and bile. The importance of these neutralizing substances is apparent because of the readiness with which ulceration occurred after their removal.

It would be interesting to observe the changes which take place in the jejunum during the first few hours of perfusion with acid and pepsin. In our experiments bleeding usually started within a few minutes and continued for a variable length of time. We have no knowledge of the factors responsible for the provocation and cessation of this phenomenon.

In the chronic experiments the ulceration differed from that usually observed in man in that it occurred

in the fundus of the stomach. However, the most severe ulceration developed along the lesser curvature, the region where gastric ulcer most often occurs in the human. The chronic experiments were similar to those performed by Mann and Bollman (1932) on dogs. They reported that about 4 weeks after the administration of acid, subacute and chronic ulcers formed near the lesser curvature of the stomach. These investigators confined their study to the effect of acid and never used a solution of pepsin in acid. Bassers (1925) introduced pepsin and acid into the stomach of dogs and sacrificed the animals after 1 to 3 days' experimentation. He found profuse ulceration of the stomach at autopsy.

Both the acute and the chronic experiments serve to emphasize the importance of pepsin in the etiology of ulceration of the gastro-intestinal tract. Since pepsin is such an important factor, we are of the opinion that the term "acid ulcer," as sometimes used in the literature, is a misnomer. It is not merely a question of terminology that is involved; the expression "acid ulcer" carries with it certain implications that may be misleading. Almost every agent at present used in the clinical treatment of peptic ulcer is an anti-acid. Consequently in such treatment there may be a chance of producing an alkalosis. Moreover, the functioning of the digestive system may be disturbed because of the lack of the normal acid stimulus for pancreatic and biliary secretion. The results here presented would seem to indicate that more attention should be paid to the inactivation of pepsin as part of the treatment of peptic ulcer. Some of the aluminum compounds precipitate and otherwise inacti-



Fig. 4. Stomach and duodenum after 8 days during which pepsin and acid were introduced daily.

vate pepsin as well as buffering the acid in the gastric juice (Schiffriu and Komarov, 1941.)

### SUMMARY

1. In both acute and chronic experiments on anesthetized and unanesthetized cats, respectively, perfusion of a segment of the gastro-intestinal tract with pepsin in an acid medium produced more severe ulceration than perfusion with acid alone.

2. The threshold of peptic activity necessary for ulceration of the jejunum was found to be 58-100 Mett units, which is within the range of peptic activity of normal canine gastric juice.

3. The maximum ulceration occurred with pepsin when it was employed in a medium having a pH within the optimum range for peptic digestion.

4. These observations emphasize the importance

of the proteolytic action of gastric juice as an etiological factor in peptic ulcer.

5. The duodenum, in the absence of pancreatic and biliary secretions was more susceptible to the action of acid alone than was either the jejunum or ileum.

We wish to express our appreciation of the invaluable advice and criticism which we have received from Professor B. P. Babkin, who directed this work. We also wish to thank Dr. T. R. Waugh, of the Pathological Institute, McGill University, for his assistance in interpreting the histological preparations.

### REFERENCES

- Dragstedt, L. R.: *J. A. M. A.*, 68:330, 1917.  
 Dragstedt, L. R. and Matthews, W. B.: *Am. J. Physiol.*, 105:29, 1933.  
 Langenskiold, F.: *Skand. Arch. Physiol.*, 31:1, 1913.  
 Mann, F. C. and Bollman, J. L.: *J. A. M. A.*, 99:1576, 1932.  
 Matthes, M.: *Beitr. Path. Anat. Allg. Path.*, 13:309, 1893.  
 McCann, J. C.: *Arch. Surg.*, 19:600, 1929.  
 Rüssers, J. R. F.: *Klin. Wochr.*, 4:644, 1925.  
 Schiffriu, M. J.: *Proc. Soc. Exp. Biol. Med.*, 45:592, 1940.  
 Schiffriu, M. J. and Komarov, S. A.: *Am. J. Dig. Dis.*, 8:215, 1941.  
 Schiffriu, M. J. and Warren, A. A.: *Am. J. Physiol.*, 133, p. 437, 1941.

## Editorial

### THE RESISTANCE OF THE GASTRIC AND INTESTINAL MUCOSA TO HYDROCHLORIC ACID AND ARTIFICIAL GASTRIC JUICE

SOME of the most interesting and perhaps most important work on the problem of ulcer production in the stomach and duodenum was done first by Matthes in 1893, later by Langenskiold in 1913, and later by Mann and Bollman in 1932. These men all studied the resistance of the gastric and upper intestinal mucosa to hydrochloric acid of a strength about that found in the dog's stomach. Much of the article of Langenskiold was translated and published in the August, 1940, number of this Journal by Dr. Lerner.

Unfortunately, the experiments of Matthes and Langenskiold were few and not entirely in agreement. The work of Mann and Bollman was much more satisfactory and complete and showed that the mucosa of the stomach and bowel can stand contact with hydrochloric acid for only a certain length of time, after which its powers of resistance become exhausted, and inflammation and ulceration appear. The work of several investigators also suggested that the resistance of the mucosa of the bowel varies inversely as the distance from the pylorus. Still another suggestion from some of this work is that the presence of food or of a peptic digest in contact with the gastric or intestinal mucosa can serve to protect it from erosion by hydrochloric acid.

These observations were of tremendous interest if only because some persons with ulcer have noted that if they take food the minute pain appears they get

good relief, whereas if they wait for an hour or two, relief may be imperfect and transitory.

Because of the importance of this type of work, the paper of Schiffriu and Warren published in this number of the Journal is of much interest. These experimenters have repeated and carried further some of the experiments of their predecessors in this field. Using cats, they have run acid or a pepsin-acid mixture through segments of the gastro-intestinal tract. They conclude that the addition of pepsin produces a more severe ulceration than is obtainable with acid alone. As one would expect, the maximal ulceration seen was obtained with pepsin in a medium having a pH within the optimal range for peptic digestion.

The present work throws doubt on the idea of a graded susceptibility of the intestinal mucosa to gastric juice. Schiffriu and Warren believe that the duodenal mucosa, in the absence of pancreatic and biliary secretions, is more susceptible to the action of acid than is either the jejunum or ileum. This point is of so much interest to gastric surgeons that more work should soon be done on it.

W. C. A.

### CORRECTION

The address of the authors of the article "Proctoscopic Cinematography" appearing on page 140 of the April, 1942 issue was erroneously given as Trenton, New Jersey. The addresses should be as follows:

J. F. Pessel, Trenton, N. J.

J. M. Garner, Winnetka, Ill.

J. Peerman Nesselrod, Chicago, Ill.

## Abstracts of Current Literature

FRANKLIN HOLLANDER, Associate Editor in Charge of Abstracts, New York, N. Y.

ALBERT CORNELL, New York, N. Y.  
MAURICE FELDMAN, Baltimore, Md.  
CHARLES A. FLOOD, New York, N. Y.  
M. H. F. FRIEDMAN, Philadelphia, Pa.  
J. DUFFY HANCOCK, Louisville, Ky.  
THOMAS A. JOHNSON, Philadelphia, Pa.  
ALLEN A. JONES, Buffalo, N. Y.  
N. W. JONES, Portland, Ore.  
HENRY H. LERNER, Boston, Mass.  
PHILLIP LEVITSKY, Montreal, Can.

JESSIE LOVE, Louisville, Ky.  
FRANZ J. LUST, New York, N. Y.  
IRA A. MANVILLE, Portland, Ore.  
ARTHUR E. MEYER, Brooklyn, N. Y.  
FRANCIS MURPHY, Milwaukee, Wis.  
H. NECHLES, Chicago, Ill.  
FRANK NEUWELT, Gary, Indiana  
SAM OVERSTREET, Louisville, Ky.  
J. F. PESSEL, Trenton, N. J.  
DAVID J. SANDWEISS, Detroit, Mich.

RUDOLPH SCHINDLER, Chicago, Ill.  
MICHAEL SHUTKIN, Milwaukee, Wis.  
VIRGIL E. SIMPSON, Louisville, Ky.  
H. J. SIMS, Denver, Colo.  
HENRY TUMEN, Philadelphia, Pa.  
ROBERT TURELL, New York, N. Y.  
EDGAR WAYBURN, San Francisco, Calif.  
JOHN WILLARD, Philadelphia, Pa.  
C. WILMER WIRTS, Philadelphia, Pa.

Microfilm copies of papers may be obtained from Microfilm Service of the Army Medical Library at 25c for each complete article, not exceeding 25 pages in length—and 10c for each additional 10 pages or fraction thereof. Prepayment is not requested. Remittance may be made with subsequent orders and in such manner as found most convenient. Address—Microfilm Service, Army Medical Library, Washington, D. C.]

### CLINICAL MEDICINE STOMACH

KOENIG, E. C. AND CULVER, G. J.: *Hodgkin's Disease Involving the Stomach*. Am. J. Roent. Rad. and Therapy, 46:827, Dec., 1941.

The authors report two cases of Hodgkin's Disease of the stomach. One a male, aged 56 years, in which the stomach revealed a large irregular defect of the distal half of the stomach, with a large gastric residue. The other a female, aged 27 years, in which there was an irregular filling defect with rigidity of the pylorus and a moderate gastric residue. There are no differentiating signs from other infiltrating ulcerating lesions involving the stomach. In both cases the diagnosis was made by histologic studies. Most of the reported cases revealed that the pylorus is the most frequent site of involvement. The cases are generally diagnosed as that of carcinoma.—Maurice Feldman.

JONES, C. M.: *Hiatus Esophageal Hernia*. New Eng. J. Med., 225:963, Dec. 18, 1941.

This paper is an exceedingly fine handling of the problems of hiatus esophageal hernia. It should be read in its entirety to be appreciated. The author reviews his clinic and private cases. He discusses the background, mechanism, and treatment of this entity. The similarity of its symptoms to angina is discussed and the diagnostic differences pointed out.—H. H. Lerner.

SANDERS, G. B. AND MECRAY, P. M.: *Pseudogastritis of Operative Origin*. Ann. Surg., 114:986, Dec., 1941.

"The incidence of gastritis reported from different clinics and from different countries varies widely. Schindler and his coworkers, suggested that the gastritis observed was an artefact produced by the technic of gastric resection in the presence of free hydrochloric acid.

"In the present work it was demonstrated that when free acid was present in the stomach of the dog, gastric changes were (1) proportional to the degree of gastric vascular engorgement which occurred during operation; and (2) to the time elapsed between beginning the resection and the examination of the specimen. The technic of gastrectomy as employed in surgical clinics can reproduce these conditions.

"The present work seems to indicate that gastroscopy rather than the study of surgically resected specimens should be the basis for the evaluation of the frequency of the coexistence of peptic ulcer and gastritis."—Thomas A. Johnson.

BLAISDELL, JACK AND ROUSUCK, A. ASHLEY: *New Gastro-Intestinal Suction-Irrigation Device*. Am. J. Surg., 55:177, Jan., 1942.

The authors have devised a new gastro-intestinal suction-irrigation apparatus. The effect of the irrigating device is comparable to that of a lavaging agent and has been found most valuable in washing out the stomach in post-operative vomiting or in poison cases. The suction

can be easily regulated as desired so that no damage can occur to the mucosal surface of the bowel by too great a pull.—Robert Turell.

### BOWEL

ROSSER, CURTICE: *The Exteriorization of Colonic Cancer*. Southern Surg., 10:874, Dec., 1941.

The trend towards primary resection of colonic tumors has been encouraged by the good results experienced in tumors of the rectum and rectosigmoid and by the recent addition of oral sulfanilylguanidine in pre-operative care. Graded exteriorization procedures are, however, much safer, certainly for lesions above the recto-sigmoid. Most of such lesions, including many on the right side present evidence of obstruction, and resection in the face of unrelieved obstruction is fatal. Measures to attempt relief of obstruction include the insertion of a catheter through the tumor from below and the use of a Miller-Abbott tube from above. Over fifty per cent of the cases should be operable by exteriorization and liver involvement is not a contraindication since in those who survive operation death is delayed and is much less distressing. The usual objections to this type of operation are not well founded. The dangers of skin implants is lessened by immediate removal of the tumor and the restriction of the amount of tissue excised is limited only by the timidity of the surgeon. The necessarily longer period of disability can be reduced by using a collar of vaseline gauze around the clamp to permit the opening of the colostomy at the end of twenty-four hours, the application of the crushing clamp within seven to twelve days after the operation, the removal of that clamp after only three or four days, and prompt surgical closure of the fistula particularly where it is above the sigmoid and spontaneous closure is not likely to occur.—J. Duffy Hancock.

DANIELS, G. E.: *Psychiatric Aspects of Ulcerative Colitis*. New Eng. J. Med., 226:178, Jan. 29, 1942.

The author reports his experience in studying twenty-five cases of ulcerative colitis during the last ten years. He finds that these patients tend to have certain common characteristics. These consist of a fixation on some member of the family. When a conflict threatens to develop such as an engagement or marriage, or child birth there is very often a prompt onset of the illness.—H. H. Lerner.

ROSSIEN, A. X.: *Intussusception*. Am. J. Roent. Rad. and Therapy, 46:832, Dec., 1941.

Rossien reports a case in a female aged 31 years, of a retrograde type of intussusception, in which the transverse colon was intussuscepted into the hepatic flexure; it was a case of chronic spontaneous reducing and relapsing type. The etiological factor in this case was a fibrous band. The roentgen examination revealed the head of the barium meal at the end of 48 hours is located at the hepatic flexure; at the site of the delay, there was a convexity at the proximal end of the transverse portion of

## A Clinical Roentgenological Review of the Literature for 1941, Pertaining to the Digestive Tract

By

MAURICE FELDMAN, M.D.  
BALTIMORE, MARYLAND

A REVIEW of the available 1941 literature with a brief appraisal of what is valuable pertaining to the clinical roentgenological aspects of the digestive tract is summarized. It is an almost impossible task to review every medical periodical that has been published during the year, however, nearly all of the outstanding contributions in the important journals were reviewed and the major advances are herewith recorded.

### ESOPHAGUS

The esophagus is influenced by various neurological and psychosomatic phenomena, such as emotion, spasm, paralysis, etc. Hysteria and other emotional episodes have long been known to produce esophageal symptoms. In recent years various potent drugs have been utilized, which are known to affect either the parasympathetic or sympathetic nerves. Faulkner and his associates (47) have studied the effect of emotions upon esophageal function and observed that it may produce severe esophageal symptoms, such as spasm and dysfunction which are indistinguishable from those of organic nature. It is noteworthy to direct attention to the Porter-Vinson syndrome or siderophrenia, which produce a dysphagia as a result of an anemia. A number of contributions have been published in recent years on this subject. Johnstone (83) reported four cases in women of menopausal age, with spasm of the crico-pharyngeus muscles, associated with anemia and dysphagia. Reports on the use of potent specific drugs on some esophageal disturbances have been studied in recent years by many workers. It has long been known that nitrites have a decided effect on the relief of spasm and muscular relaxation. Certain nitrites, for instance, have a decided effect upon cardiospasm which offer some temporary relief. In recent years prostigmine has been used in various muscular dystrophies and spastic states with good effect. Meyer and Necheles (109) have shown that prostigmine increases the peristalsis and tonus, thus increasing esophageal contractions and emptying of the esophagus in cases of cardiospasm. Schwab and his associates (140) in their studies of the effect of prostigmine in cases of mysathenia gravis point out that dysphagia occurs in about 60 per cent of cases and that prostigmine relieves the dysphagia due to this condition, but emphasizes that those due to other causes, such as bulbar palsy, do not respond to this drug. The association of many abnormalities with cardiospasm have been recorded on numerous occasions. Herniation of the dilated esophagus into the abdomen, displacing the stomach, has rarely been recognized. Ball and Crump (9) reported such an instance.

Numerous cases of congenital atresia of the esophagus have been published in the recent literature. The majority of cases of atresia are associated with fistula. The roentgen demonstration of the fistulous tract is not often shown. Ashley (7) reports an instance in which lipiodol was injected into the trachea, revealing the tracheo-esophageal fistula, with opaque media in the stomach. Of interest are the cases of tracheo-esophageal fistula without the presence of esophageal obstruction. Gengenbach and Dobos (57) in a report of ten cases of tracheo-esophageal fistula mention three cases in which there was no esophageal obstruction associated with the fistula. Fistulous formation of the esophagus as a complication of pleuropulmonary disease is uncommon and comparatively few cases have been recorded. Torbett and Bennett (152) report a case of esophagopleural fistula as a complication of empyema.

Since the advent of the Roentgen-ray in the routine gastro-intestinal studies, herniation of the stomach through the esophageal hiatus and thoracic stomach have been observed with greater frequency. The incidence of esophageal hiatus hernia of the stomach is recorded by Levy and Duggan (99) who found 26 cases in 1,220 gastro-intestinal examinations. One must especially note the length of the esophagus carefully, for at times it is difficult to precisely determine its length. It would be interesting to note the picture after relaxation of the esophagus and stomach following the administration of atropine and nitrites. Perhaps some of the cases of thoracic stomach may yet prove to be cases of hernia of the cardia of the stomach with a normal length esophagus. Thoracic stomach is not uncommonly seen and a number of single case reports are recorded. McGee (106) reported a single instance of a thoracic stomach. A rather high percentage of thoracic types of stomach was noted by Polley (126) who studied 47 cases of esophageal hiatus hernia finding a congenital short esophagus with partial or complete thoracic stomach in 14 cases. An unreported observation of the association of diverticulosis of the colon (48.4 per cent) was noted by Polley in his 47 cases of hiatus hernia and short esophagus.

Tumors of the esophagus other than carcinoma are very rare. In recent years a number of single case reports of benign tumors of the esophagus have been recorded. Most of these have been of the pedunculated type. French and Garland (55) report a case of leiomyosarcoma of the esophagus. They have been able to find only four previously reported cases. Syphilis of the esophagus is rarely recognized. It may occur in three forms, gummatous, ulcerous or infiltrative. The gummatous type may produce an esophageal obstruction. Kampmeier and Jones (85)

report four cases of gummata, one in the esophagus and three involving the diaphragm at or near the esophageal hiatus, all of which produced esophageal obstruction.

### STOMACH

The improvement in the roentgen technic for the demonstration of soft tissues in the abdomen has led to a number of publications which stressed the importance of recognizing the value of these shadows. The soft tissue shadows may be either of normal structures or neoplasms. The demonstration of the stomach without contrast media is not often visible when it is completely empty. The cardia of the stomach is frequently outlined as a rounded ball by gas, but occasionally when fluid is present, by a dense smooth rounded shadow containing fluid and gas. This shadow is a normal phenomenon.

Feldman (49) points out a new sign of pyloric obstruction, when the entire stomach is outlined as a soft tissue shadow. This is made possible by the fact that a large gastric retention of fluids is responsible for the production of this shadow. It is a well known fact that cases of achlorhydria are more prone to neoplasms than in the cases of normal or hyperchlorhydria. Carey and his associates (25) studied 233 cases of achylia gastroscopically, found 28 cases of carcinoma and 21 cases of benign gastric tumors.

This year's literature deals with further studies on gastroscopic findings in gastritis. Many studies of cases of gastritis has been correlated with gastroscopic and roentgen findings. The gastroscopic examination is the method of choice in the study of gastritis, the X-ray may frequently give results which are erroneous and often of a negative character. In a study of 150 cases by Kelley and his associates (87), they point out that it is erroneous to assume that the size and caliber of the gastric folds indicate a particular type of gastritis and further emphasize that the diagnosis of chronic gastritis should be made with great reservation. McClure et al (105) had gastroscopically studied 611 cases, found 269 cases of gastritis, of which 150 were hypertrophic, 51 atrophic and 68 superficial. Of interest in their series of cases, is the association of duodenal ulcer with hypertrophic gastritis; of 68 cases of hypertrophic gastritis, there were 20 cases of duodenal ulcer and one case of gastric ulcer. Phlegmonous gastritis is a rare condition, infrequently seen by the roentgenologist. Most of the cases reported are single instances. A pre-operative diagnosis is rarely made, although the X-ray in some instances reveal signs which may lead to a diagnosis when considered with a clinical history. Sovena (149) reported a case of acute phlegmonous gastritis which was limited to the pyloric portion of the stomach. A case of subacute phlegmonous gastritis localized in the pylorus in which the X-ray revealed a large annular smooth pyloric narrowing with an obstruction, that simulated a carcinoma was reported by Vass and Sirca (153.)

The incidence of peptic ulceration in children in recent years has been steadily increasing. This increase no doubt is due in part to the fact that more children are being X-rayed. Formerly most of the cases of peptic ulcer in children were those in which complications had occurred. Moore (112) reported 8 instances of peptic ulcer in children, 7 duodenal and 1 gastric, in all of which there were X-ray signs of

the condition. Conklin (36) reported 2 instances of peptic ulcer in children, one a duodenal ulcer disclosed by the X-ray, the other a perforated gastric ulcer. The role of site in relation to peptic ulceration has played a prominent role in the determination of the histologic nature of the lesion; thus ulcers located on the lesser curvature of the body of the stomach are more likely to be benign, while those that occur on the greater curvature are more apt to be malignant. Although this guiding rule has considerable merit, the fact that occasionally ulcers occurring on the greater curvature of the stomach may be benign should also be given some consideration. Williams (163) reported 2 proven cases of benign peptic ulcer on the greater curvature of the stomach. There have been numerous studies on the relative incidence between gastric and duodenal ulcer. There seems to be a variance of incidence between the radiologic and autopsy findings. McMullen (107) in 883 cases of peptic ulcer diagnosed radiographically, revealed that 78 per cent were duodenal and 22 per cent gastric. On the other hand, it has been shown, a number of years ago by Portis and Jaffe, that pathologic findings in consecutive autopsies have shown that gastric ulcer slightly predominates. Complications of peptic ulcer occur with great frequency. The most common are those due to perforation. Griswold and Antoncic (69) analyzed 111 cases of perforated peptic ulcer of which 102 were operated upon; 56 were duodenal, 45 were gastric and one jejunal. They noted the presence of free air in the peritoneal cavity in 73 per cent of 97 cases examined. Of unusual interest is the complication of duodenal ulcer by an obstructive jaundice. Scott (141) reported an instance in which the perforation of a duodenal ulcer located in the second portion of the duodenum, directly over the common duct produced a distention and edema of the wall causing pressure which resulted in jaundice. A more or less unusual complication of gastric ulcer is the formation of a fistula. Steigmann and Bach (150) report two cases of gastro-duodenal fistula, one of the fistulas led to the duodenal cap, the other into the fourth portion of the duodenum. Obstruction of the gastrojejunal stoma is not an uncommon finding. It usually denotes the presence of edema or stricture due to a secondary ulceration. Hoag and Saunders (76) point out that obstructions at the stoma are probably more common after gastro-enterostomy than after some of the more radical procedures. Harper and Wilson (72) report a case of duodenal stasis complicating a gastrojejunal ulcer.

Diverticula of the stomach are not uncommonly seen in the routine roentgen studies of the gastro-intestinal tract. They are now being recognized with greater frequency than in previous years. They have certain roentgen characteristics which are more or less pathognomonic, though often they simulate an ulcer niche. It is important to recognize the diverticulum because of the fact that they may at times become complicated by inflammation or perforation. Reich (129) reported 8 cases, 6 of which he found in 19,022 gastric examinations. Reineke (130) reported four cases and Schmidt and Walters (139) reported 3 cases.

Syphilis of the stomach is not uncommon. The pre-operative diagnosis is at times extremely difficult, es-



pecially when the clinical data are excluded. When one must depend upon the finding of the spirochete the incidence is very low. Avent (8) reported a case in which there was an obstruction between the body and fundus of the stomach produced by syphilis. In his case the specimens did not reveal spirochetes, but the Wassermann reaction was positive.

Many comprehensive studies on congenital pyloric stenosis have been presented in the literature. Of interest is the genetic basis as an etiologic factor in the production of this condition. Ford et al (54) reported a case of pyloric stenosis in both members of two pairs of male twins. They noted that in 436 cases of pyloric stenosis there were twelve pairs of twins. O'Donnell and Klein (121) in a report of pyloric stenosis in non-identical twins, also lends additional evidence to support the theory of hereditary pathogenesis of pyloric stenosis. There has been considerable discussion in the literature as to the value of the X-ray in the diagnosis of congenital pyloric stenosis. Some pediatricians do not believe that the X-ray is of any value, while others find it of considerable importance. Calvin and Denenholz (23) in 105 operated cases give the following data to support the importance of the X-ray in the diagnosis of pyloric stenosis, point out that the relative amount of barium passed out of the stomach after four hours is a definite criteria. They noted that 92.3 per cent revealed a retention of from 60 to 100 per cent. In 78 cases in which a roentgen diagnosis was made, it was correct in 98.8 per cent. It was further pointed out that in pylorospasm 91.3 per cent showed a 25 per cent or less retention in the stomach after four hours.

Tumors of the stomach arising from connective tissue have recently been recorded with greater frequency. Yardumian and Swickley (166) in a study of 122 cases of gastric tumors found 115 carcinomas, 2 benign epithelial tumors and 5 non-epithelial tumors. The incidence of smooth muscle tumors of the stomach is low, yet it occurs with greater frequency than is believed. The ratio of smooth muscle tumors of the gastro-intestinal tract is given by Golden and Stout (62) as follows: the stomach was involved in 61 per cent, small intestine 19 per cent, rectum 7 per cent, duodenum 5 per cent and the colon in 3 per cent. Of interest in smooth muscle tumors is their tendency to bleed in about 50 per cent of cases. They may be benign or malignant.

Christopher et al (28) report an instance of malignant leiomyoma in a child. Rumold (135) reported a case of submucous lipoma of the stomach. Morton and Burger (115) report two cases of hemangioma of the stomach. One of the rarer types of benign tumors of the stomach are the fibromas. These tumors also tend to ulcerate and hemorrhage. Basile (13) reported an instance of fibroma of the stomach. Of unusual interest is a case reported by Cohn and his associates (32) of a small granuloma in the stomach produced by the administration of colloidal kaolin (hydrated aluminum silicate.) The authors have experimentally produced similar tumors in rabbits. The most common neoplasm of the stomach is carcinoma. Many contributions have been published on this subject during the year, most of which were of statistical value. Saypol and Hinton (137) in 122 cases of carcinoma of the stomach have shown the importance of the X-ray as a means of recognizing the condition.

They emphasize the fact that a correct diagnosis was made in 116 of the 122 cases.

Gray (66) discussed the malignant potentiality of gastric ulcer, pointed out that it is impossible to distinguish positively between simple gastric ulcer from an early carcinomatous ulcer. He emphasized the fact that the niche may even occasionally decrease in size or may even disappear in the presence of malignant change. Lymphoid tumors of the gastro-intestinal tract are now being recognized and reported with greater frequency. There has been an increasing number of publications on this subject during the past year. The stomach is the most common site for lymphoid tumors. Koenig and Culver (92) report two cases of Hodgkin's disease of the stomach, both involving the pylorus which produced gastric retention. Cameron et al (24) encountered two cases of primary sarcoma of the stomach, one an endo-gastric spindle cell sarcoma, the other a lymphosarcoma. Hochman (77) reported two cases. A case of liposarcoma is reported by Abrams and Turberville (2), which involved the pylorus and produced obstructive signs. Giere (59) reported a case of lymphosarcoma of the stomach, stressed the gastrosopic findings. There are but few recorded cases of complications occurring in sarcoma of the stomach. Koucky et al (94) report a case of acute perforation of a lymphosarcomatous ulcer of the stomach. Most complications associated with malignant neoplasms of the stomach are of the chronic type with fistulous formation. In 12 cases of gastroduodenal fistula reported by Ritvo and McDonald (132) 5 were due to tumors, 4 of which were malignant and one undetermined.

## DUODENUM

Little consideration has been given to the normal interior of the duodenum. Feldman (50) described the roentgen appearance of the interior of the second portion of the duodenum in some detail, discussed the normal mucosal folds, and duodenal papilla. The roentgenologic consideration of duodenal ulceration has received some attention during the past year. However, much of the information adduced is of statistical value. Ordinarily a large proportion of cases of duodenal ulcer show a small niche defect which is best demonstrated by the compression technic. These ulcers are readily detected and offer no difficulty in diagnosis. However, the roentgen picture of a giant ulcer of the duodenal bulb may be misinterpreted, because the size of the ulcer crater may simulate a normal duodenal bulb. Elkin (46) reports a case of a giant duodenal ulcer, found 10 other such cases and of these 6 were misinterpreted.

Duodenal diverticula are rather common. The majority arise in the second portion on the inner border, in the periampullary region. They are usually single. Weintraub and Tuggle (159) studied 310 cases, found that 52 of the cases revealed a retention, and that 66 per cent arose in the second portion of the duodenum. It is interesting to note that in 14 of the cases which came to autopsy none revealed any pathology in the diverticulum. The fact that a retention in the diverticulum may occur suggests the possibility that secondary complications may arise in these diverticulae. Although duodenal diverticula are as a rule comparatively small in size, they may become large enough to produce pressure on the adjacent organs. Ogilvie



(122) reported 4 cases in which a diverticulum produced an obstruction of the pancreatic duct, causing pancreatic necrosis.

Tumors of the duodenum are very rare. They are usually single and may arise from any portion of the duodenum. Henning and Garland (74) report a case of leiomyosarcoma of the third portion of the duodenum. Syphilis of the duodenum is unusually rare and it is almost impossible to make a diagnosis. The possibility of syphilis producing a stenosis of the duodenum is remote. Hernandez-Morales and Ruiz-Cestero (75) report an unconfirmed case of syphilis of the duodenum producing a filling defect in the second portion close to the bulb, resulting in a large gastric retention which had completely disappeared following luetic therapy.

### INTESTINES

There have been a number of radiologic and anatomic studies of the terminal portion of the ileum during the past year. Last (101) studied the mucosal arrangements, noted transverse folds in the pelvic ileum and a longitudinal arrangement in the prececal segment. Meckel's diverticulum is not generally recognized until some complication occurs. Numerous surgical emergencies result from involvement of Meckel's diverticulum, namely, hemorrhage, perforation, intussusception, obstruction, volvulus, inflammation, etc. Chaffin (26) reported 19 cases of Meckel's diverticulum which produced surgical emergencies during childhood. Conrad (37) reported 2 cases, one with gangrene and torsion of the diverticulum, the other with bleeding. Tumors are rarely observed in Meckel's diverticulum. A case of perforated leiomyoma, which had occurred at the tip of the diverticulum is reported by Koucky and Beck (93.) Congenital giant diverticula of the intestine other than Meckel's diverticulum or reduplication is exceedingly rare. It usually occurs in the lower ileum and may also contain heterotopic gastric mucosa and cause hemorrhage and perforation. Such a case has been reported by Duckett (42.)

Jejunal diverticulitis is not often recognized; it is usually found at operation or at autopsy. Koziun and Jennings (95) report a case of a gangrenous diverticulum of the jejunum with peritonitis. Atresia of the terminal portion of the ileum with perforation was reported by Moses (116.) He pointed out that the roentgenogram will reveal evidence of a stenosis, or when perforation occurs, air will be seen in the peritoneal cavity. Numerous reports on regional ileitis have been recorded in the 1942 literature, most of which are of statistical value. Some points in diagnosis were emphasized; for instance, Eckel and Ogilvie (43) noted that of 13 cases X-rayed, 11 were diagnosed correctly; the string sign was observed in only 6 of these cases. Graham (65) reported 35 cases of regional ileitis, points out that in none did he find a fistula. Of 413 cases collected by Graham, the terminal ileum was involved alone in 63.2 per cent and the terminal ileum and adjacent bowel in 93.4 per cent.

Tumors of the small intestine are difficult to recognize until some complication occurs. A number of reports have been published in the past year concerning neoplasms of the small intestine. Doub and Jones (41) reported 33 cases of neoplasms of the small intestine of which 25 were malignant and 8 were benign. Of the 8 benign tumors 3 occurred in the duodenum,

while of the 25 malignant tumors 13 had occurred in the duodenum. Morison (114) reported 13 cases of benign and 4 malignant tumors of the small intestine. White (161) recorded a case of hemangioma of the terminal ileum which had produced recurrent hemorrhages. Horsley (78) reported two cases of carcinoma of the small intestine, while Hunt and Kaneh (81) report 3 cases, all occurring in the jejunum. Sarcoma of the small intestine, one of the rarer forms of neoplasms occurring in the small bowel, is not often seen. The diagnosis cannot, as a rule, be made preoperatively. Clont (27) reported 8 cases of small intestinal tumors found in 24,693 surgical specimens; of these there were 3 leiomyomas, 1 leiomyosarcoma, 3 lymphosarcomas and 1 carcinoma. Shulman (145) reported a case of lymphosarcoma of the jejunum, which caused a moderate delay through the affected segment and other signs, which may be produced by any type of neoplasm.

Attention has been directed in the recent literature to surgical emergencies of childhood. These are of special interest to the gastro-enterologist and the radiologist, because of the diagnostic factors involved. Congenital obstructions of the small intestine occur with some frequency in infants. Wikle (162) reports a case of obstruction at the duodeno-jejunal junction due to an extrinsic cause. Cohen (31) reported 8 cases of intestinal obstruction in infants, emphasizes the use of the plain film in the diagnosis. Mayo and Woodruff (103) reported 55 cases of acute intussusception, 65 per cent of whom were less than one year of age. In 53 of these, no causative factor was found, while the remaining 2 cases were due to Meckel's diverticulum. Kahle (84) in an analysis of 151 cases showed that 59.5 per cent occurred in children under two years of age; the majority being of the ileocecal or ileocolic type. An unusual case in his series is one of a retrograde ileo-ileal intussusception.

The chronic and recurrent types of intussusception are more commonly seen in adults. These are generally due to neoplasms, especially the pedunculated variety. An unusual adult case of retrograde intussusception is reported by Rossien (134), which produced a chronic spontaneous reducing and relapsing type, caused by a fibrous band. Good (64) reported 3 cases occurring in the lower ileum due to a tumor and one case involving the lower ileum caused by Meckel's diverticulum. Coleman et al (33) report a case of recurring jejunal intussusception in which no tumor was found. Botsworth and Newton (16) report a case in an adult due to a submucous lipoma of the ileum. Kirkman et al (90) record a case of ileo-cecal intussusception in an adult due to a small polyp. Levitin (98) shows two interesting cases which were diagnosed by the X-ray without contrast media. The findings consisted of a gas distended loop within which there was a smaller sized gas filled loop. Abrams (1) likewise noted a case in which the plain roentgenogram revealed a sausage-shaped soft tissue mass surrounded by air. In this case there were several small linear gas collections and a similar curved area with its convexity upward, findings which are believed to be due to an intussusception of the terminal ileum.

Reports on acute intestinal obstruction have been noted in numerous publications. Of particular interest

are those cases caused by gall stone, which frequently present a characteristic roentgen picture, which is diagnostic of the condition. The diagnosis may be made by the demonstration of the gall stone or the visualization of air in the biliary tract. Rigler and his associates (131) reviewed 404 cases of intestinal obstruction, found that 11 cases were due to gall stones. Cahill (22) reported a case in which a gall stone caused an obstruction at the sigmoid flexure. The etiology of intestinal obstruction is at times difficult to determine. The presence of obstruction in women should require a pelvic examination to determine the presence of an endometrosis. This condition has a tendency to migrate to other structures and at times involves the colon. Numerous case reports of endometrosis of the colon have been noted in the literature of the past year. Rarely is the small intestine involved. Grigsby (68) reported two cases of endometrial implants in the ileum. Patton and Patton (124) record a case of endometrosis of the sigmoid with obstruction. Lefrancois (96) reported a case involving the sigmoid and Blaikley (15) a case producing an annular stricture of the pelvic colon.

Another important cause of intestinal obstruction is that due to mesenteric vascular occlusion. Moore (113) directed attention to a diagnostic point, in his report of 8 cases in which he gives one or two enemas; this often leads to the evacuation of blood-stained fluid which he believes is diagnostic. An unusual cause of intestinal obstruction is that produced by bezoars. Very few cases of this condition have been recorded. By careful roentgen technic it is possible at times to diagnose the condition. Newberger (118) reports a case of phytobezoar which produced an obstruction at the terminal ileum. A plain roentgenogram in his case revealed evidence of a paralytic ileus, but a colon enema revealed a filling defect in the terminal ileum.

Gas in the colon frequently offers considerable interference in the diagnosis of roentgen shadows, especially of the gall bladder and kidneys. The use of drugs to eliminate gas shadows has been most helpful. Lofstrom (100) studied the effect of pitressin on the digestive tract, found that it had no action on the stomach or on the normal jejunum or ileum, but when the small bowel is distended it had a pronounced effect. It likewise had no effect upon the gall bladder. Its greatest effect, however, is noted in the colon, where it increases its tonicity and collapses the lumen. Of the benign colon maladies, mucous colitis and irritable and spastic colons occur with increasing frequency. Most of the publications have been of statistical value. A spastic state of the colon is a common condition, causing either constipation or diarrhea.

Isolated cases of spasticity causing intestinal obstruction have been noted by a number of authors, but the condition is comparatively rare. Of interest is the localized spasm of a marked degree, occurring in a small segment of the colon, mainly in the descending or sigmoid colon, which may produce all of the clinical and roentgen signs of intestinal obstruction. Colp (35) reported 5 cases of large bowel obstruction produced by spasm. Simple ulcers of the colon are infrequently observed and are rarely diagnosed preoperatively. Most of these ulcers are found in the right colon and the majority have perforated before being recognized. Barlow (12) collected 78 cases, adding two of his own. The clinical and radiologic

incidence of intestinal tuberculosis does not approach that found at autopsy. Perhaps this is due to the fact that in the terminal stages of tuberculosis, intestinal involvement is found in a larger proportion of cases. Burke and Aronovitch (21) observed 99 cases dying of tuberculosis, found that in 70 there was evidence of ulcerative intestinal tuberculosis.

Carcinoid tumors are most commonly seen in the appendix. The colon is an unusual site for carcinoids. According to Waugh and Snyder (157) only 11 cases of carcinoid tumors of the colon have been reported and of these 5 were located in the cecum. When they occur in the cecum, they generally are located in the region at the base of the appendix. They may be large sized, resembling a polyp. Waugh and Snyder report a single case of carcinoid tumor of the cecum.

Diverticulosis of the colon is a common condition, occurring with greater frequency in the descending and sigmoid colon; the largest number are found in the sigmoid. Diverticulosis may at times produce an intermittent train of mild symptoms, only its complications are severe, and of these diverticulitis is the most common. Eggers (44) reported 82 cases of diverticulitis and sigmoiditis and presented the following data; pain in 100 per cent, palpable tumor in 45.2 per cent, obstruction in 29.3 per cent, perforation in 24.4 per cent, bleeding in 19.5 per cent, diarrhea in 18.3 per cent, constipation in 68.3 per cent and associated carcinoma in 6.1 per cent.

Benign tumors of the colon, although not very commonly reported, are of particular interest. There were few publications on this subject during the past year. Of the rarer forms of tumors, hemangiomas of the colon are not often recognized. Hunt (82) reported a case of hemangioma of the colon and collected 48 cases of vascular tumors of the intestine, of which 27 involved the small intestine, and 16 the rectum and sigmoid. Lipomas are likewise not often recognized. Gault and Kaplan (56), report a case of lipoma of the colon in which the X-ray revealed an obstruction in the mid-transverse colon.

Lymphogranuloma venereum involving the lower colon and rectum is an infrequent condition. It is generally a complication of venereal granulomas. Of the greatest importance is the Frei test, which is helpful in the differential diagnosis. The chronic stage is one of an ulcerating stenosing proctocolitis, with scarring, strictures, abscesses and fistulae not infrequently seen in this condition. It may be associated with carcinoma. Barber and Murphy (11) reported 55 cases involving the rectum and sigmoid. There have been numerous publications on carcinoma of the colon, but most of the reports, however, have been of statistical value. Of interest is the report by Buirge (20) who found 416 cases of carcinoma of the colon and rectum in 26,798 autopsies. Of these 67.2 per cent were located in the distal portion of the colon. In 97 cases in which roentgen studies were made, a correct diagnosis was made in 84.5 per cent; in 5.2 per cent it was uncertain; while in 10.3 per cent it was incorrect.

A number of interesting contributions on anomalies and abnormalities of the appendix have been published during the past year. A case of double appendix with a single cecum has been reported by Waugh (158) who had collected 14 similar cases from the literature.

A pre-operative diagnosis is impossible, except perhaps in rare instances is it possible for the X-ray to reveal a double appendix. In the case of appendiceal calculi, these are often radiable. A case of appendiceal calculi is reported by Guido (70), which was demonstrated by the X-ray. A case of mucocele of the appendix with rupture was reported by Ostrum and Miller (123), in which the X-ray portrayed a large calcified tumor. Of particular interest in this case were the multiple fistulae connecting the cecum, bladder, rectum, ileum and sigmoid. Intussusception of the appendix is an unusually rare condition. A case is reported by McSwain (108.) The presence of an appendix in a hernial sac is not uncommonly seen; Williams (164) reports such a case.

Internal abdominal herniae are comparatively rare. Cases have been recorded with increasing frequency during the past year. These cases are of diagnostic interest from a radiological standpoint. Numerous cases have been recognized by means of the X-ray, though the majority of cases are only diagnosed following operation. Archer and Cooper (6) report 2 cases of intra-abdominal hernia. Mayo and his associates (104) reviewed 39 cases, 10 of which were secondary to gastro-enterostomy, and 8 were duodenal. Hudson (79) reports a case of internal hernia with a volvulus of the small intestine. Cogswell and Thomas (30) report on right paraduodenal hernia, note that it comprises 53 per cent of all internal herniae. An unusual case of hernia is that reported by Paul and McAneny (125) in which the splenic flexure of the colon was found behind the spleen and produced signs of obstruction. In the past year a large number of publications have been written on diaphragmatic hernia, much of which is of statistical value only. Of interest perhaps is the report by Harrington (73) on 270 operations for various types of diaphragmatic hernias; most of these were of the esophageal hiatus type, however, there were four cases of the subcostal variety. Colmers (34) reported a case of parasternal diaphragmatic hernia.

### BILIARY TRACT

Diseases of the gall bladder and cholecystography have been discussed in numerous publications during the year. Of increasing interest is the visualization of the bile ducts and duct pathology. Doran and his associates (40) reported a series of cholecystographic studies in 147 cases in which the X-ray findings were confirmed in 124 or 84 per cent. He pointed out the well known fact that the greatest margin of error lies in the normally filled gall bladders. In 10 normal cholecystograms, stones were found in 5 cases or 50 per cent. During the cholecystographic test the hepatic ducts are not as a rule visualized, but the cystic and common ducts are frequently visible following a fat meal, when the roentgenograms are made at the proper interval. Copleman and Sussman (38) report 4 cases in which there was filling of the hepatic ducts as well as the cystic and common ducts in an otherwise normal gall bladder.

Since the advent of cholecystography, the presence of a diverticulum of the gall bladder has been observed with increasing frequency. The condition, however, is comparatively rare, as MacCarty had found only 25 specimens in 29,701 surgically removed gall bladders. Scott and his associates (142) report a case of double

gall bladder in which a double cystic duct was also found. In this case there were also two papillomas in the gall bladder.

The recognition of tumors of the gall bladder and extra bile ducts have also been observed in increasing numbers in the past year. Their recognition by means of cholecystography has enhanced the diagnostic incidence of this condition. Coate (29) reported 8 cases of tumors of the gall bladder, 4 of which were adenomas and 4 papillomas. Greenlee and his associates (67) reported 5 cases of carcinoma of the gall bladder. Kirachbaum and Kozell (91) found 55 cases of primary carcinoma of the gall bladder and 62 cases of primary carcinoma of the extra hepatic bile ducts in 3,330 autopsies, which is an unusually high incidence. The site of the ductal carcinomas were as follows: cystic duct 7 cases, hepatic duct 13 cases, common duct 32 cases, and the papilla of Vater 10 cases. River and his associates (123) reported 3 cases of carcinoma of the ampulla of Vater, while Vaughn (154) reported one case. In the ampullary carcinomas, it is pointed out that the X-ray may reveal signs of duodenal stenosis, defects in the duodenum and duodenal irritability. The clinical features of carcinoma of the papilla of Vater are described by Sharpe and Comfort (144) in 40 cases. Of interest in their report is the fact that the gall bladder was found to be normal in 7 of 10 cases in whom cholecystography was made, in spite of an existing jaundice. In a roentgen consideration of the terminal common bile duct and duodenal papilla, Feldman (51) described the changes that occur in the interior of the duodenum, such as enlargement of the papilla, enlargement of the fold and splitting of the folds surrounding the papilla.

Cholangiography has received considerable attention in recent years. It is a highly useful procedure in the exploration of the common bile duct, often yielding valuable information. MacDonald (102) studied the peristalsis of the common bile duct by fluoroscopic and serial roentgenography, visualized actual peristalsis and noted a forward propulsion of the duct contents. Altman (3) advocates the fractional method in the study of the bile duct and also recommends the use of amyl nitrite. Saralegui (136) in his studies of the bile ducts, noted that hyperperistalsis is a sign of disease of the common bile duct. He believes that when the ampulla of Vater is visualized it denotes a pathological condition. In the case of carcinoma of the ampulla of Vater the common duct is moderately dilated as a result of stenosis. Cysts of the common duct are unusually rare and are difficult to recognize. Bangerter (10) reported 2 cases of cyst of the common bile duct. Diverticula of the common bile duct, however, may be recognized by means of cholangiography. Sjögren (146) described a proven case of diverticulum of the common duct which was demonstrated by cholangiography. An interesting case of hypertrophy of the sphincter choledochus was reported by Boyden (17) in which 3 large gall stones were impacted in the lower end of the common bile duct. The stone telescoped the major papilla and protruded into the lumen of the duodenum producing a fistula. Spontaneous internal biliary fistula have been noted with increasing frequency in the past year. These cases are of especial interest to the roentgenologist.

because they can be recognized by the presence of air in the biliary tract and by occasionally a radiable gall stone. It may be emphasized, however, that a negative X-ray does not exclude a biliary fistula. Eliason and Stevens (45) described 5 cases which were found among 15,677 operations. Fernicola and Tenconi (53) report a case of fistula between the gall bladder and the duodenum in which cholecystographic studies revealed a normal gall bladder, but following a barium meal a small amount of barium entered the gall bladder.

### PANCREAS

The pancreas has been a topic of considerable importance during the past year. The diagnosis of pancreatic diseases has not attained the same degree of accuracy as that of some of the other digestive organs. This is especially true in the early stages of pancreatic pathology. The pancreas does not lend itself to direct examination and most of the roentgen signs are secondary. The association of changes in the head of the pancreas with duodenal ulceration has long been known. Recently Feldman (52) reported 7 cases of enlargement of the head of the pancreas, in which he observed signs of pressure in the second portion of the duodenum, in the form of an inverted three; in five of the cases there was evidence of duodenal ulceration. Walters and Cleveland (156) report on 255 cases of pancreatic lesions, in which 185 were malignant and 70 were benign. Of the latter cases 28 were due to pancreatitis, 22 cysts, 4 adenoma, 3 hyperinsulinism, and 9 cases of accessory pancreas. Of the 9 cases of accessory pancreas 90 per cent revealed the anomalous pancreas in the stomach, duodenum or jejunum; the largest number being in the duodenum; with 6 per cent in the ileum and 2 per cent in Meckel's diverticulum. A subject which has accumulated a considerable literature in the past year is the islet cell tumor or insulinoma or adenoma of the islet cells of the pancreas. These tumors are usually small in size and are rarely larger than the size of a walnut, but occasionally they may attain considerable size. The small sized tumors are not recognized by the X-ray and do not, as a rule, present a palpable mass. In the majority of cases there is a hyperinsulinism with a characteristic glucose tolerance curve. A small percentage of the islet cell tumors of the pancreas become malignant and tend to metastasize. Brunschwig (19) reported a case which presented the largest sized tumor as yet reported, measuring 15 cm. in diameter. The mass containing small calcified shadows, was demonstrated by the X-ray. Vayo and Bodou (155). Meyer et al (110). Windfield (165) have contributed publications on this subject.

Reports on carcinoma of the pancreas have been increasing in recent years. Most of these reports have been of statistical value, but a few, however, have presented a number of interesting diagnostic features. Carcinoma of the pancreas lends itself indirectly to X-ray studies because of its close relation to the stomach and duodenum; it produces signs of pressure which are often more or less characteristic. Often the X-ray signs are incorrectly interpreted. Berk (14) studied 31 cases, found that in 37 per cent the X-ray signs were positive, but when the X-rays were re-studied after operation, the reviewed films yielded positive findings in 64.5 per cent. Ochsner (120) has presented an interesting roentgen sign, which he had

noted in 3 cases of carcinoma of the head of the pancreas associated with duodenal diverticulum. He found a rotation and upward displacement of the diverticulum with flattening of the inferomedial surface. Kauer and Glenn (86) found 38 cases of carcinoma of the pancreas in 28,600 hospital admissions. Intravenous cholecystography will reveal a normal gall bladder shadow in approximately one-third of the cases and an abnormal shadow in two-thirds of the cases. The abnormality most commonly seen is poor concentration, dilatation, and failure of the gall bladder to empty. In Kauer and Glenn's series of 38 cases, cholecystography was made in 6 of the cases, and in 5 of these there was a non-filling and in one it was normal.

The finding of gall stones associated with cancer of the head of the pancreas is not infrequent. The ratio of gall stones in cancer of the pancreas and that of cancer of the gall bladder is about 1 to 18. In Kauer and Glenn's 38 cases, only five revealed the presence of gall stones. Cyst-adenocarcinoma of the pancreas is rare; Kennard (89) found 3 cases among 6,708 autopsies. Pancreatic lithiasis has also shared in the increasing reports on pancreatic disease. A number of publications are found in the past year's literature. The condition lends itself well for roentgen diagnosis, as the stones mostly contain calcium carbonate, which is opaque to the X-ray. They are usually multiple and most commonly found in the pancreatic ducts. Snell and Comfort (148) reviewed 18 cases. Poppel and Levy (127) and Smith and Bonis (147) each report 3 cases.

### LIVER

It is impossible to diagnose accurately by X-ray most of the diseases of the liver. However, there are a few conditions which may be recognized. Arce (5) reports on hydatid cysts of the liver, which he points out produces an enlargement of the liver. Its presence is often revealed by calcifications within the cyst. Schatzki (138) reporting on the roentgen diagnosis of carcinoma of the liver, found 15 cases in 4,323 autopsies. He describes the roentgen signs in detail in 4 cases and emphasizes that in 87 per cent of the cases there is an associated cirrhosis of the liver with concomitant varices of the esophagus. A number of reports on subphrenic abscess are noted in the year's literature, most of which have only been of statistical value. Faxon (48) presented a statistical study on subphrenic abscess, noted that the condition was on the right side in 84 per cent and left side in 16 per cent of the cases. He stressed the position of the diaphragm in the X-ray studies; found it elevated in 78 per cent and not elevated in 4 per cent, not visible in 18 per cent; fluid level and gas were observed in 29 per cent of the cases. Golding and Delario (63) point out the difficulty encountered in the diagnosis of left sided subphrenic abscess.

### MISCELLANEOUS

Transposition of the viscera is a comparatively uncommon congenital anomaly. All of the organs are usually involved, but in rare instances it may be segmental. Anton and his associates (4) report a case of segmental abdominal heterotaxy. A case of retractile mesenteritis associated with early carcinoma of the gall bladder was reported by Rademaker (128),

in which there was an abdominal mass recognized by the X-ray, which pushed the duodenum to the right. Hancock (71) reported 2 cases of mesenteric tumors, one due to carcinoma, the other a lymphangioma. Seids and Hauser (143) report 2 cases of aneurysm of the splenic artery. These occasionally reveal calcifications which become visible on the X-ray. A case of ruptured aneurysm of the celiac artery is reported by Le Vay (97), which produced a large mass in the right hypochondrium. Nutter and his associates (119) report on giardia lamblia infection, point out that in their cases the gall bladder did not play a significant part. In those cases in which cholecystography was done, the test revealed a normal gall bladder shadow. The belief has frequently been expressed that biliary symptoms are generally associated with giardiasis. Others have reported having observed non-filling gall bladders in the cholecystographic test, in many cases of giardiasis.

Golden (60-61) presented a comprehensive study on the abnormalities of the small intestine in nutritional disturbances and Vitamin B deficiencies, discussed in detail the pathologic and roentgen changes resulting from the atrophy caused by these conditions. In the early cases he noted hypermotility and hypertonicity while in the more advanced stages, there was hypomotility and hypotonicity, abnormal segmentation and dilatation of the intestine with gas and fluid levels, changes in the mucosal folds and gastric retention. Hueblein and his associates (80) direct attention to the effect of Vitamin B complex on gastric emptying and small bowel motility, found that reduction in muscle tone is the outstanding feature of Vitamin B

deficiency. Gershon-Collen et al (58), found various grades of hypomotility, atonicity, hypotonicity, stasis and dilatation of the intestine in Vitamin B avitaminosis.

The occurrence of gastro-intestinal disturbances in thyroid disease has been known for many years. The changes noted are those of motility and tonicity. Brown and his associates (18) report on the gastro-intestinal tract in hyperthyroidism, point out that the most striking phenomena occur in the small intestine, with changes in the mucosal pattern. They noted that the herringbone pattern is finer and may be replaced by an "iron filling type" of pattern. The production of gastro-intestinal disturbances by allergic conditions is not often recognized, but occurs quite often. Golden believes that it may produce a deficiency pattern in the intestine. Thomas and Wofford (151) discuss the clinical findings in 134 cases of gastro-intestinal allergy, point out the nature of the intestinal symptoms.

It is with considerable pride that one must compliment the many authors who have contributed to the past year's literature on the subject of digestive diseases. Their continued interest as evidenced by their frequent publications is noteworthy. There were numerous reviews of various phases of the digestive tract published during the past year that are of immense value and many interesting facts were brought to light. The statistical value of the many reports are highly important, and the countless case reports of interesting and unusual conditions are important to record so that the accumulated data may offer some aid to others in the recognition of these affections.

## REFERENCES

1. Abrams, H. S.: Intussusception; Particular Reference to Roentgen Diagnosis Without opaque Media. *Radiology*, 36:493, 1941.
2. Abrams, M. J. and Turberville, J. H.: Liposarcoma of the Stomach. *Southern Surgeon*, 19:261, 1941.
3. Altman, W. S.: Cholangiography; Fractional Method. *Radiology*, 37:261, 1941.
4. Anton, J. L., Panoff, C. E. and Spiegel, M. H.: Segmental Abdominal Heterotaxy. *Am. J. Surg.*, 64:443, 1941.
5. Aree, José: Hydatid Cysts of the Liver. *Arch. Surg.*, 42:915, 1941.
6. Archer, V. W. and Cooper, G. Jr.: Intra-Abdominal Hernia. *Radiology*, 36:453, 1941.
7. Ashley, J. D. Jr.: Congenital Atresia of the Esophagus with Tracheo-esophageal Fistula. *Radiology*, 36:521, 1941.
8. Avent, C. H.: Syphilis of the Stomach Necessitating Total Gastrectomy. *Surgery*, 9:571, 1941.
9. Ball, R. P. and Crump, A. C.: Mega-Esophagus (Cardiomegaly) Report of a Case with Subdiaphragmatic Herniation of the Esophagus. *Radiology*, 35:575, 1941.
10. Banerjee, J.: Idiopathic Cholelithiasis Cyst. *Schweiz. med. Wochenschr.*, 71:677, 1941.
11. Barber, W. H. and Murphy, W. B.: Lymphogranuloma Venereum. *Ann. Surg.*, 113:39, 1941.
12. Barlow, D.: Simple Ulcers of the Cecum, Colon and Rectum. *Brit. J. Surg.*, 28:573, 1941.
13. Basile, A.: Fibroma of the Stomach. *Ann. ital. di chir.*, 20:79, 1941.
14. Berk, J. E.: Diagnosis of Carcinoma of the Pancreas. *Arch. Int. Med.*, 69:525, 1941.
15. Blakely, J. H.: Endometrioma of the Colon Causing Stricture. *Proc. Roy. Soc. Med. Sect. Obst. and Gyn.*, 34:510, 1941.
16. Botwinow, T. W. and Newton, F. C.: Intussusception in an Adult Due to Submucous Lipoma of the Ileum. *Surgery*, 10:263, 1941.
17. Boyden, E. A.: Hypertrophy of the Sphincter Cholelithiasis: a Cause of Internal Biliary Fistula. *Surgery*, 10:567, 1941.
18. Brown, R. B., Pendergrass, E. P. and Hurdick, E. D.: The Gastro-Intestinal Tract in Hyperthyroidism. *S. G. O.*, 78:776, 1941.
19. Brunschwig, A.: Large Islet Cell Tumor of Pancreas. *Surgery*, 9:554, 1941.
20. Buirge, E. E.: Carcinoma of the Large Intestine. *Arch. Surg.*, 42:801, 1941.
21. Burke, H. E. and Aronovitch, M.: Intestinal Tuberculosis. *Canad. Med. Ass'n J.*, 45:21, 1941.
22. Cahill, J. A. Jr.: Obstruction of the Sigmoid Flexure by a Large Gall Stone. *Am. J. Surg.*, 52:255, 1941.
23. Calvin, J. K. and Denenholz, E. J.: Value of Roentgenography in Congenital Pyloric Stenosis. *Arch. Pediatr.*, 58:26, 1941.
24. Cameron, A. L., Brodick, P. J. and Minot, N. D.: Primary Sarcoma of the Stomach. *Surgery*, 9:916, 1941.
25. Carey, J. B., Wetherby, M. and Ylvisaker, R. S.: Some Observations in Achlorhydria. *Am. J. Dig. Dis.*, 8:401, 1941.
26. Chaffin, L.: Surgical Emergencies During Childhood Caused by Meckel's Diverticulum. *Ann. Surg.*, 113:47, 1941.
27. Cheet, L. H.: Sarcoma of the Small Intestine and Reference to Their Radioreactivity. *Radiology*, 34:51, 1941.
28. Christopher, F., Benjamin, E. L. and Sauer, I. W.: Lymphoma Malignum of the Stomach. *Surgery*, 10:351, 1941.
29. Coote, J. D.: Roentgenologic Demonstration of Tumors of the Gall Bladder. *Am. J. Roent. and Rad. Ther.*, 46:229, 1941.
30. Cowdell, H. D. and Thomas, C. A.: Right Paraoduodenal Hernia. *Ann. Surg.*, 114:1035, 1941.
31. Cohen, P.: Congenital Intestinal Obstruction: with Special Reference to the Value of the Plain Roentgenogram for Diagnosis. *Am. J. Dis. Child.*, 61:155, 1941.
32. Cohn, A. L., White, A. S. and Weyrauch, H. H.: Kaposi Granuloma of the Stomach. *J. Am. Med. Ass'n*, 117:225, 1941.
33. Coleman, F. B., Maguire, R. H. and Bennett, D. A.: Recurring Jejunal Intussusception. *Am. J. Surg.*, 53:340, 1941.
34. Colmers, R. A.: Parasternal Diaphragmatic Hernia: with Report of a Case on the Right Side. *Radiology*, 37:733, 1941.
35. Colp, R.: Colonic Spasm as a Cause of Intestinal Obstruction. *Surgery*, 10:270, 1941.
36. Conklin, C. B.: Peptic Ulcer in Children. *Internat. Clin.*, 2:73, 1941.
37. Conrad, H. A.: Meckel's Diverticulum: Report of Two Cases. *Am. J. Surg.*, 52:267, 1941.
38. Copleman, B. and Susman, M. L.: Hepatic Duct Visualization Following Oral Cholecystography. *Radiology*, 36:453, 1941.
39. D'Elia, A. S.: Pneumogastroscopy: a Preliminary Report. *Am. J. Surg.*, 53:250, 1941.
40. Doran, W. T., Hansen, E. C. and Lewis, K. M., Spier, L. C. B. and Doran, W. T., Jr.: Gall Bladder Surgery. *Ann. Surg.*, 53:11, 1941.
41. Douthett, P. and Jones, H. C.: The Roentgenologic Diagnosis of Tumors of the Small Bowel. *Am. J. Dis. Dig.*, 8:148, 1941.
42. Duckett, J. W.: Giant Diverticulum or Duplication of the Intestine with Recurrent Perforations. *Ann. Surg.*, 112:525, 1941.
43. Eckel, J. H. and Ogilvie, J. V.: Regional Enteritis: Report of 21 Cases. *Am. J. Surg.*, 53:345, 1941.
44. Ervoss, C.: Acute Diverticulitis and Sigmoiditis. *Ann. Surg.*, 113:16, 1941.
45. Ellison, F. L. and Stevens, L. W.: Spontaneous Internal Biliary Fistula. *Am. J. Surg.*, 51:387, 1941.
46. Elkin, W. P.: Diagnostic Problems in Cases of Large or Giant Duodenal Ulcer. *Radiology*, 37:748, 1941.
47. Faulkner, W. B., Rosenbaum, F. H. and O'Neill, J. R.: Influence of the Emotions Upon Esophageal Function: a Comparison of Esophagoscopy and Roentgenologic Findings. *Radiology*, 37:443, 1941.
48. Faxon, H. H.: Subphrenic Abscess. *Am. J. Surg.*, 54:114, 1941.
49. Feldman, M.: A New Roentgen Sign of Pyloric Obstruction: the Visualization of the Stomach Without the Use of Contrast Media. *Radiology*, 36:736, 1941.
50. Feldman, M.: A Roentgenologic Consideration of the Normal Mucosa of the Duodenum. *Radiology*, 37:254, 1941.



51. Feldman, M.: The Terminal Common Bile Duct and Duodenal Papilla. *S. G. O.*, 73:388, 1941.
52. Feldman, M.: Slight Enlargement of the Head of the Pancreas: Associated with Pathologic Changes in the Duodenum. *Radiology*, 36:224, 1941.
53. Fernicola, C. and Tenconi, E.: Roentgenological Diagnosis of a Spontaneous Fistula Between the Gall Bladder and the Duodenum Caused by a Biliary Calculus. *Rev. asoc. med. argent.*, 53:35, 1941.
54. Ford, N., Brown, A. and McCreary, J. F.: Evidence of Monzygosity and Disturbance of Growth in Twins with Pyloric Stenosis. *Am. J. Dis. Child.*, 61:41, 1941.
55. French, L. R. and Garland, L. H.: Leiomyosarcoma of the Esophagus. *Am. J. Roent. and Rad. Ther.*, 45:27, 1941.
56. Gault, J. T. and Knipian, P.: Submucous Lipoma of the Colon. *Am. J. Surg.*, 53:145, 1941.
57. Gezenbrech, F. P. and Dobos, E. I.: Congenital Tracheoesophageal Fistula. *J. Pediatr.*, 19:444, 1941.
58. Gershon-Cohen, J., Shay, H. and Fels, S. S.: B<sub>12</sub> Avitaminosis: Roentgenologic Studies of the Gastro-Intestinal Tract in Rats on Vitamin B<sub>12</sub> Deficiency Diets. *Am. J. Roent. and Rad. Ther.*, 46:876, 1941.
59. Gierke, C. N.: Lymphosarcoma of the Stomach. *J. Am. Med. Assn.*, 117:173, 1941.
60. Golden, R.: Abnormalities of the Small Intestine in Nutritional Disturbances. *Radiology*, 36:262, 1941.
61. Golden, R.: The Small Intestine in Vitamin B Deficiency. *J. Am. Med. Assn.*, 117:213, 1941.
62. Golden, R. and Stout, A. P.: Smooth Muscle Tumors of the Gastro-Intestinal Tract and Retroperitoneal Tissues. *S. G. O.*, 73:34, 1941.
63. Golding, H. and Delario, A. J.: Left Subphrenic Abscess. *Radiology*, 36:161, 1941.
64. Good, C. A.: Chronic Intussusception of the Small Intestine. *Proc. Staff Meet. Mayo Clinic*, 16:324, 1941.
65. Graham, W. L.: Regional Ileitis. *Canad. Med. Ass'n J.*, 44:168, 1941.
66. Gray, H. K.: Carcinoma of the Stomach. *J. A. M. A.*, 116:22, 1941.
67. Greenlee, D. P., Hamilton, R. C. and Ferraro, F. P.: Primary Carcinoma of the Gall Bladder. *Arch. Surg.*, 42:598, 1941.
68. Grigsby, G. P.: Endometriosis as a Cause of Intestinal Obstruction. *Southern Surgeon*, 10:8, 1941.
69. Griswold, R. A. and Antonice, R. F.: Perforated Peptic Ulcer. *Ann. Surg.*, 113:191, 1941.
70. Guido, F. R.: Appendiceal Calculus. *Calif. and West. Med.*, 75:19, 1941.
71. Hancock, J. D.: Mesenteric Tumors. *Southern Surgeon*, 10:569, 1941.
72. Harper, F. R. and Wilson, R. E.: Duodenal Stasis Complicating Gastrojejunal Ulcer. *Am. J. Surg.*, 52:140, 1941.
73. Harrington, S. W.: Subcostal Diaphragmatic Hernias. *S. G. O.*, 73:501, 1941.
74. Henning, B. H. and Garland, L. H.: Leiomyoma of the Duodenum. *Radiology*, 37:353, 1941.
75. Hernandez-Morales, F. and Ruiz-Cestero, G.: Syphilis of the Duodenum. *Am. J. Dig. Dis.*, 5:362, 1941.
76. Hoag, C. L. and Saunders, J. B.: Obstruction Following Gastro-Enterostomy or Subtotal Resection of the Stomach. *Arch. Surg.*, 42:253, 1941.
77. Hochman, A.: Sarcoma of the Stomach. *Lancet*, 1:362, 1941.
78. Horsley, J. S.: Carcinoma of the Jejunum and the Ileum. *J. A. M. A.*, 117:2119, 1941.
79. Hudson, H. W., Jr.: So-Called Mesentericoparietal Hernia. *New Eng. J. Med.*, 225:4, 1941.
80. Huebner, G. W., Thompson, W. D. and Scully, J. P.: The Effect of Vitamin B Complex Deficiency on Gastric Emptying and Small Bowel Motility. *Am. J. Roent. and Rad. Ther.*, 46:866, 1941.
81. Hunt, E. L. and Kaneb, G. D.: Primary Adenocarcinoma of the Jejunum. *New Eng. J. Med.*, 224:355, 1941.
82. Hunt, V. C.: Hemangioma of the Large Bowel. *Surgery*, 10:651, 1941.
83. Johnstone, A. S.: Some Radiological Observations on Post-Cricoid Obstruction and Anemia. *Brit. J. Radiol.*, 14:177, 1941.
84. Kahle, H. R.: An Analysis of 151 Cases of Intussusception from the Charity Hospital in Louisiana at New Orleans. *Am. J. Surg.*, 52:215, 1941.
85. Kampmeier, R. H. and Jones, E.: Esophageal Obstruction Due to Gummatous of the Esophagus and Diaphragm. *Am. J. Med. Sci.*, 201:539, 1941.
86. Kaver, J. T. and Glenn, F.: Carcinoma of the Pancreas. *Arch. Surg.*, 42:141, 1941.
87. Kelley, C. H., Lawlah, J. W. and Berry, L. H.: Mucosal Relief Technic Correlated with Gastroscopy in 150 Cases. *Radiology*, 36:77, 1941.
88. Kelley, R. W.: Duodenal Obstruction; Unusual Types. *Southern Med. J.*, 34:471, 1941.
89. Kennard, H. E.: Papillary Cystadenocarcinoma of the Pancreas. *Surgery*, 9:165, 1941.
90. Kirkman, N. F., Barlow, T. and Mottershead, S.: A Case of Persistent Intussusception in an Adult. *Brit. J. Surg.*, 28:426, 1941.
91. Kirshbaum, J. D. and Kozoll, D. D.: Carcinoma of the Gall Bladder and Extrahepatic Bile Ducts. *S. G. O.*, 73:740, 1941.
92. Koenig, E. C. and Culver, G. J.: Hodgkin's Disease Involving the Stomach. *Am. J. Roent. and Rad. Ther.*, 46:827, 1941.
93. Koucky, J. D. and Beck, W. C.: Perforated Leiomyoma of Meckel's Diverticulum. *Surgery*, 10:636, 1941.
94. Koucky, J. D., Beck, W. C. and Atlas, J.: Acute Perforation of Lymphosarcomatous Ulcer of the Stomach. *Ann. Surg.*, 114:1112, 1941.
95. Kozinn, P. J. and Jennings, K. G.: Jejunal Diverticulitis: Its Occurrence in a Two Year Old Child. *Am. J. Dis. Child.*, 62:620, 1941.
96. Lefrançois, C.: A propos d'un cas d'endometrose du colon sigmoïde. *J. de l'Hôtel-Dieu de Montreal*, 10:40, 1941.
97. Le Vay, A. D.: Aneurysm of the Coeliac Artery. *Brit. J. Surg.*, 28:502, 1941.
98. Levitin, J.: Ileocolic Intussusception: Diagnosis Without Contrast Media. *Am. J. Surg.*, 64:494, 1941.
99. Levy, M. D. and Duggan, L. B.: Hiatus Hernia of the Stomach. *South. Med. J.*, 34:351, 1941.
100. Lofstrom, J. E.: Further Observations on Elimination of Intestinal Gas Shadows in Roentgenography. *Radiology*, 36:334, 1941.
101. Lust, F. J.: Roentgenological Studies of the Mucosa of the Normal Terminal Ileum. *Am. J. Roent. and Rad. Ther.*, 45:63, 1941.
102. MacDonald, D.: Common Bile Duct Peristalsis. *S. G. O.*, 73:564, 1941.
103. Mayo, C. W. and Woodruff, R.: Acute Intussusception. *Southern Surgeon*, 10:583, 1941.
104. Mayo, C. W., Stalker, L. K. and Miller, J. M.: Intra-Abdominal Hernia. *Ann. Surg.*, 114:875, 1941.
105. McClure, C. W., Sweetser, F. N. and Jankelson, I. R.: Chronic Gastritis. *New England J. Med.*, 225:259, 1941.
106. McGee, H. H.: Thoracic Stomach. *Am. J. Roent. and Rad. Ther.*, 45:69, 1941.
107. McMullen, J. W.: A Roentgenologic Study of the Relative Incidence of Gastric and Duodenal Ulcer. *Radiology*, 37:194, 1941.
108. McSwain, B.: Intussusception of the Appendix. *Southern Med. J.*, 34:263, 1941.
109. Meyer, J. and Necheles, H.: Cardiospasm: Observations on the Use of Prostigmine. *J. Lab. and Clin. Med.*, 27:162, 1941.
110. Meyer, K. A., Amtman, L. and Perlman, L.: Islet Cell Tumors of the Pancreas. *J. A. M. A.*, 117:116, 1941.
111. Montgomery, M. M. and Kirshbaum, J. D.: Jejunal (Anastomotic) Ulcer. *Arch. Int. Med.*, 67:609, 1941.
112. Moore, O. M.: Peptic Ulcer in Children. *Canad. Med. Ass'n J.*, 44:462, 1941.
113. Moore, T.: Mesenteric Vascular Occlusion. *Brit. J. Surg.*, 28:347, 1941.
114. Morison, J. E.: Tumors of the Small Intestine. *Brit. J. Surg.*, 29:139, 1941.
115. Morton, C. B. and Burger, R. E.: Hemangioma of the Stomach. *Surgery*, 10:821, 1941.
116. Moses, E.: Atresia of the Terminal Portion of the Ileum with Perforation in a Premature Infant. *Am. J. Dis. Child.*, 62:141, 1941.
117. Navasquez, S. De.: Nutritional Oedema as a Complication of Jeuno-Colic Fistula. *Brit. J. Surg.*, 28:468, 1941.
118. Newberger, B.: Intestinal Obstruction Due to Phytobezoar. *Rev. Gastro-Enterol.*, 8:293, 1941.
119. Nutter, P. B., Rodaniche, E. C. and Palmer, W. L.: Giardiasis Infection in Man. *J. A. M. A.*, 116:1631, 1941.
120. Ochsner, H. C.: The Roentgenological Diagnosis of Periduodenal and Extraduodenal Lesions. *Am. J. Roent. and Rad. Ther.*, 45:718, 1941.
121. O'Donnell, F. T. and Klein, J. M.: Pyloric Stenosis in Non-Identical Twins. *Am. J. Dis. Child.*, 62:1025, 1941.
122. Ogilvie, R. F.: Duodenal Diverticula and Pancreatic Necrosis. *Brit. J. Surg.*, 28:362, 1941.
123. Ostrum, H. W. and Miller, R. F.: Calcified Mucocele of the Appendix, with Rupture. *Radiology*, 36:356, 1941.
124. Patton, C. L. and Patton, R. J.: Endometriosis of Sigmoid as a Cause of Acute Intestinal Obstruction. *Am. J. Surg.*, 53:265, 1941.
125. Paul, L. W. and McAneny, J. B.: Herniation of the Splenic Flexure of the Colon Behind the Spleen. *Radiology*, 36:230, 1941.
126. Polley, H. F.: Congenital Short Esophagus with Thoracic Stomach and Esophageal Hiatus Hernias. *J. A. M. A.*, 116:821, 1941.
127. Poppel, M. H. and Levy, A. H.: Pancreatic Lithiasis. *Radiology*, 37:174, 1941.
128. Redemker, L.: A Case of Retroile Mesenteritis Associated with Early Carcinoma of the Gall Bladder. *Am. J. Surg.*, 52:115, 1941.
129. Reich, N. E.: Gastric Diverticula. *Am. J. Dig. Dis.*, 7:70, 1941.
130. Reineke, H. G.: Diverticula of the Upper End of the Stomach. *Am. J. Roent. and Rad. Ther.*, 46:650, 1941.
131. Rixler, L. G., Borman, C. N. and Noble, J. F.: Gall Stone Obstruction. *J. A. M. A.*, 117:1753, 1941.
132. Rivo, M. and McDonald, E. J.: Gastro-colic Fistula. *Radiology*, 37:269, 1941.
133. River, L., McNesly, R. W. and Ragins, A. B.: Carcinoma of Ampulla of Vater. *Am. J. Surg.*, 52:289, 1941.
134. Rossini, A. X.: Intussusception. An Adult Case. *Am. J. Roent. and Rad. Ther.*, 46:832, 1941.
135. Rumold, M. J.: Submucous Lipoma of the Stomach. *Surgery*, 10:242, 1941.
136. Saralegui, J. A.: Roentgen Findings in the Exploration of the Bile Ducts. *Am. J. Roent. and Rad. Ther.*, 45:360, 1941.
137. Snypol, G. M. and Hinton, J. W.: Statistical Review of Carcinoma of the Stomach. *Am. J. Surg.*, 54:431, 1941.
138. Schatzki, R.: Roentgenologic Diagnosis of Primary Carcinoma of the Liver. *Am. J. Roent. and Rad. Ther.*, 46:476, 1941.
139. Schmidt, H. W. and Walters, W.: Diverticula of the Stomach. *Am. J. Surg.*, 52:315, 1941.
140. Schwab, R. S. and Viets, H. R.: Roentgenoscopy of the Pharynx in Myasthenia Gravis Before and After Prostigmine Injection. *Am. J. Roent. and Rad. Ther.*, 45:357, 1941.
141. Scott, A. C.: Obstructive Jaundice Caused by Perforating Duodenal Ulcer. *Southern Surgeon*, 10:637, 1941.
142. Scott, W. R., Sannes, S. and Smith, H. A.: Cholecystographic Diagnosis of Double Gall Bladder with Pathologic Verification. *Radiology*, 37:492, 1941.
143. Seids, J. V. and Huser, H.: Aneurysm of the Splenic Flexure. *Radiology*, 36:171, 1941.
144. Sharpe, W. S. and Comfort, M. W.: Carcinoma of the Papilla of Vater. *Am. J. Med. Sci.*, 202:238, 1941.
145. Shulman, S.: Primary Lymphosarcoma of the Jejunum. *Am. J. Roent. and Rad. Ther.*, 46:182, 1941.
146. Sjögren, S. E.: A Diverticulum-Like Formation of the Common Bile Duct, Demonstrated by Cholangiography. *Acta Radiol.*, 22:318, 1941.
147. Smith, E. E. and Bonis, A.: Pancreatic Lithiasis. *Am. J. Roent. and Rad. Ther.*, 46:64, 1941.
148. Snell, A. M. and Comfort, M. W.: The Incidence and Diagnosis of Pancreatic Lithiasis. *Am. J. Dig. Dis.*, 8:237, 1941.



149. Sorensen, E.: Phlegmonous Gastritis. *Polliclinico. (sez. chir.)*, 45: 199, 1941.
150. Steigmann, F. and Bach, A. C.: Peptic Ulcer and Gastro-Duodenal Fistulae. *Am. J. Surg.*, 52:355, 1941.
151. Thomas, J. W. and Wofford, C. P.: Gastro-Intestinal Allergy. *Am. J. Dig. Dis.*, 5:311, 1941.
152. Torbett, J. W. and Bennett, A. C.: Esophagopleural Fistula: Complication of Empyema. *Am. J. Surg.*, 52:129, 1941.
153. Vars, A. and Sircu, D. M.: Localized Subacute Phlegmonous Gastritis, Simulating Pyloric Carcinoma. *Am. J. Roent. and Rad. Ther.*, 46:59, 1941.
154. Vaughn, A. M.: Primary Carcinoma of the Ampulla of Vater. *Am. J. Surg.*, 52:482, 1941.
155. Vayo, P. G. and Bodon, G. T.: Adenoma of Langerhans Islet of the Pancreas. *Am. J. Surg.*, 54:744, 1941.
156. Walters, W. and Cleveland, W. H.: Surgical Lesions of the Pancreas. *Arch. Surg.*, 42:919, 1941.
157. Waugh, J. M. and Snyder, J. M.: Carcinoid Tumor of the Cecum. *Proc. Staff. Meet. Mayo Clinic*, 15:689, 1941.
158. Waugh, T. R.: Appendix Vermiformis Duplex. *Arch. Surg.*, 42:311, 1941.
159. Weintraub, A. and Tuggle, A.: Duodenal Diverticula. *Radiology*, 36:297, 1941.
160. Weisel, W. and Walters, W.: Diverticulosis of the Gall Bladder. *Proc. Staff Meet. Mayo Clinic*, 16:753, 1941.
161. White, R. J.: Hemangioma of the Terminal Ileum with Recurrent Hemorrhages from the Rectum. *Southern Surgeon*, 10:886, 1941.
162. Wikle, H. T.: Congenital Obstruction of the Small Intestine. *Am. J. Surg.*, 51:429, 1941.
163. Williams, A. J.: Peptic Ulcer of the Greater Curvature of the Stomach. *Radiology*, 37:746, 1941.
164. Williams, E. R.: Appendicular Hernia. *Brit. J. Radiol.*, 14:41, 1941.
165. Windfield, P.: Surgical Treatment of Pancreatic Adenomas Producing Insulin. *Ugeskrift f. Læger*, Copenhagen, 103:352, 1942.
166. Yardumian, K. Y. and Swickley, I. B.: Primary Non-Epithelial Tumors of the Stomach. *Am. J. Surg.*, 52:346, 1941.

## Hidradenitis Suppurativa: Diagnosis and Treatment of its Perianal Manifestations

By

RAYMOND J. JACKMAN, M.D.\*  
ROCHESTER, MINNESOTA

**H**IDRADENITIS suppurativa is a chronic inflammatory disease of the skin and subcutaneous tissue which affects those portions of the cutaneous surface of the body in which the apocrine sweat glands are located; namely, the axillary, mammary, inguinal, genital and perianal regions. It is characterized by the formation of abscesses, sinuses and ulceration and by undermining of the sites of predilection.

The importance of the disease to the proctologist or the surgeon is that its perianal manifestations are not uncommonly confused with those of anal fistula, pilonidal cyst or other conditions which produce chronic sinus formation in this region. As an entity hidradenitis suppurativa has failed to receive recognition in current text books on proctology or on surgery.

In 1939 Brunsting (1) published a report of a comprehensive study of the disease and pointed out that the condition is much more common than generally is appreciated. It has been obscured under such names as "abscess" or "furunculosis of the axillas or buttocks," "pyoderma," "fistulous disease of the buttocks" and "nonspecific granuloma." In 1938 Smith (2), in reporting a group of six cases of pyoderma simulating extensive anal fistula, explained that superficial examination in each case suggested the presence of an extremely complicated anal fistula. More careful study, however, failed to reveal any evidence which would substantiate such a diagnosis. Verneuil (3, 4) a French surgeon, who first described the disease almost a century ago, recognized through clinical observation alone the association of abscesses with the location of the apocrine sweat glands.

The apocrine sweat glands originate from the hair follicles and usually do not become active until puberty. These glands are probably vestigial remnants of scent glands which in some animals are thought to be associated with sexual attraction. In contradis-

tinction, the eccrine or ordinary sweat glands are derived from the epidermis and are distributed over almost the entire skin. The apocrine sweat glands are larger than the eccrine and normally are found in the skin of the axillary, mammary, inguinal, genital and perianal regions, the sites of predilection of the disease.

Hidradenitis suppurativa is a disease of adults usually occurring in the second and third decades and afflicting robust persons who have a seborrhic type of skin and associated acne. The cause is obscure, but the disease is infectious and is associated with a variety of bacteria, which may reach the apocrine glands by different routes. At an early stage the disease is characterized by the formation of a solitary abscess, simulating a furuncle. In a more advanced stage suppuration, burrowing, undermining, and formation of sinuses develop. Cases have been reported in which extension and burrowing continued into the anal canal thus producing anal fistula. It is much more likely, however, that if a true anal fistula exists, it is purely coincidental and without relation to the disease itself. In the twenty-two cases which Brunsting reported, the perianal region was involved in twelve. In one of the twenty-two cases, the perianal region alone was involved, the other sites of predilection showing no evidence of the disease.

Histologically, in hidradenitis suppurativa the apocrine sweat glands reveal primary involvement in an inflammatory reaction. The infection spreads by means of the lymphatic channels and tissue spaces throughout the skin and subcutaneous tissue. Eventually the affected glands may become destroyed. As the inflammatory reaction progresses from the suppurative stage, associated with the presence of polymorphonuclear leukocytes and lymphocytes, to the chronic stage, associated with draining sinuses, ulceration and undermining, an attempt at healing is manifest, as

\*Section on Proctology, Mayo Clinic, Rochester, Minn.  
Submitted January 30, 1942.

evidenced by fibrosis, granulation, and relatively little cellular infiltration (Figs. 1 and 2.)

### DIAGNOSIS

The diagnosis of the perianal manifestations of hidradenitis suppurativa is usually not difficult, if the disease is thought of, in cases of what appears to be extensive anal fistula with many sinuses. In most instances the other sites of predilection show some evidence of involvement. However, the perianal manifestations of the disease may be confused with any other condition which produces an inflammatory reaction or chronic sinus formation in this region. Several of the patients seen at the clinic had been treated for extensive anal fistula, pilonidal disease and

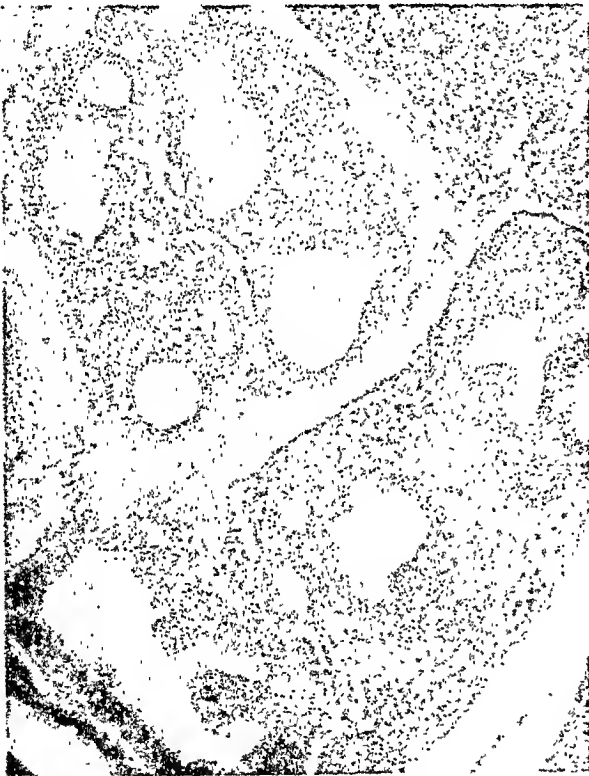


Fig. 1. Early stage of hidradenitis suppurativa in which the apocrine sweat glands are still apparent although there is infiltration of lymphocytes and polymorphonuclear leukocytes around them.

lymphogranuloma venereum. In one case diagnosis of actinomyces had been made.

In each case, study of the history, clinical observation, examination of anal and perianal regions with the patient under anesthesia, specific intradermal skin tests, demonstration of the infectious organism and biopsy may be necessary to make a differential diagnosis. Very rarely does the process of burrowing and sinus formation of the disease enter the anal canal itself, and if it does, the region of involvement is likely to be well distal to the dentate margin, whereas all true anal fistulas have their origin at the dentate margin. Perhaps it is the sinus formation of this disease which has given rise to the so-called "incomplete external fistula" (Fig. 3.)



Fig. 2. Late stage with sinus formation. The squamous epithelium is absent in the region of the sinus.

### TREATMENT

In general, treatment for hidradenitis suppurativa may be divided into two types: the conservative and the radical. In the early stage of the disease, incision and drainage of the individual abscess and the use of

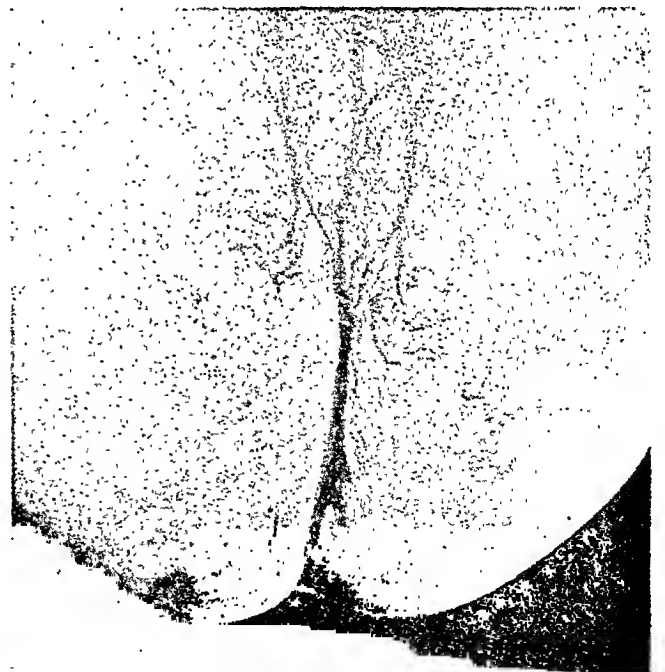


Fig. 3. Late-stage of the disease with deep induration, multiple sinuses, the involvement extending forward on labia and inner aspect of thighs. The anal canal itself was free of any evidence of the disease and the dentate margin was normal.

Roentgen-rays are the two most valuable methods at the disposal of the physician. When the disease is far advanced and has failed to respond to conservative measures, excision of the involved tissue and plastic repair may be necessary. Macey (5) described a method of dealing with the axillary involvement which amounts to excision of all of the involved tissue, use of a split-skin graft and prevention of contracture.

In the perianal and perineal regions where it is difficult or impossible to produce a wound which will not be contaminated and where one is not so concerned about some scarring and contracture as in the axilla, the procedure is altered somewhat. In general the same principles are maintained in dealing with the perianal manifestations of hidradenitis suppurativa as in carrying out other anorectal surgical procedures; that is, excision of the involved tissue and the production of adequate drainage. The excision is carried out by dissection en bloc, which should include any fibrous or inflamed portions of the subcutaneous fat and connective tissues. All sinuses and epithelial skin bridges should be explored and excised, producing clean, superficial wounds without overhanging edges, so that during the stage of healing epithelization can take place readily from the edges. Post-operatively the denuded areas are treated the same as potentially infected wounds; that is, hot moist packs, mild aqueous antiseptics, sulfathiazole powder and so forth are employed. Frequently, before healing is complete, excision of excessive granulation tissue may be necessary. Since 1936, eleven patients who had perianal or perineal manifestations, or both; scrotal and inguinal manifestations of the disease have been treated in this manner at the clinic with very satisfactory results. In one case it was necessary subsequently to excise several small regions of recurrent infection in skin adjacent to the site of primary involvement; at the time of the original surgical treatment the adjacent skin had been felt to be normal. When the denuded area is very extensive, skin grafting, either with full-thickness pedicle grafts or with split-skin grafts, may be necessary (Fig. 4a and b.)

#### COMMENT

It has been my purpose in this discussion to call the attention of those physicians who are particularly interested in rectal diseases to the perianal manifestations of hidradenitis suppurativa. Patients suffering from this condition frequently consult the proctologist first, and when they do so, much time and effort can be saved if the possibility of the disease is kept in mind. The differential diagnosis is not difficult. Surgical excision with or without skin grafting offers these patients a good prognosis.

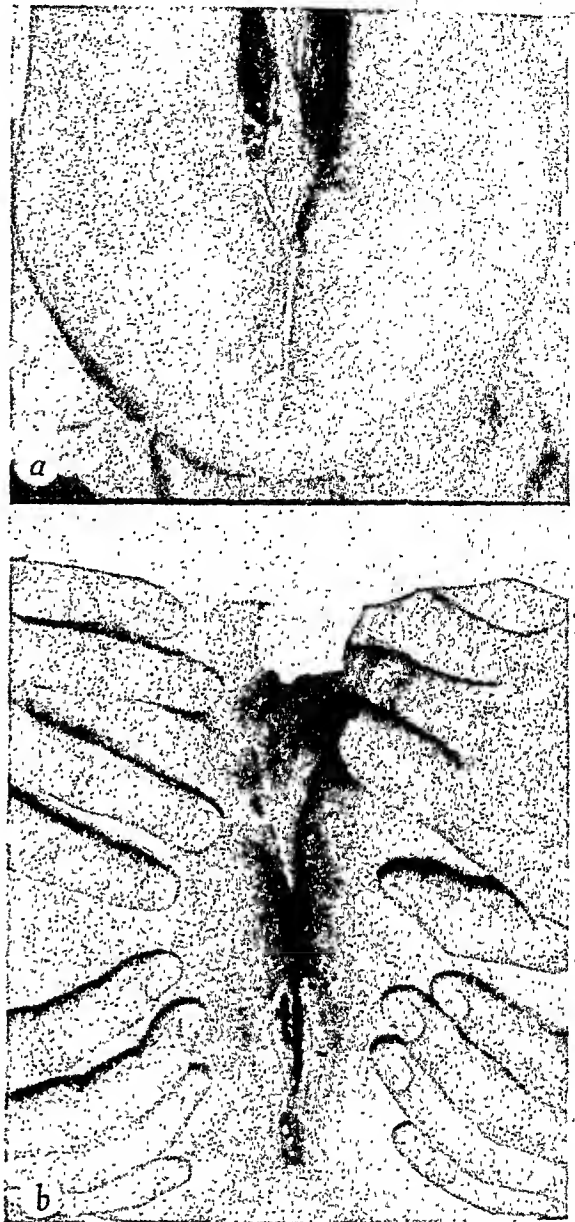


Fig. 4a and b. Post-operative result; healing almost complete after extensive scalping type of operation; minimal scarring and deformity.

#### REFERENCES

1. Brunsting, H. A.: Hidradenitis Suppurativa; Abscess of the Apocrine Sweat Glands; a Study of the Clinical and Pathological Features, with a Report of Twenty-Two Cases and a Review of the Literature. *Arch. Dermat. and Syph.*, 39:108-119, Jan., 1939.
2. Smith, N. D.: Pyoderma Simulating Extensive Anal Fistula. *Tr. Am. Proct. Soc.*, 39:163-176, June, 1938.
3. Verneuil, A.: Etudes sur les tumeurs de la peau; de quelques maladies des glandes sudoripares. *Arch. gén. de méd.*, 21:447-468, Oct.; 693-705, Dec., 1854.
4. Verneuil, A.: De l'hidrosadénite Phlegmoneuse et des abscesses sudoripares. *Arch. gén. de méd.*, 114:537-557, Nov., 1864; 115:327-337, March; 437-453, April, 1865.
5. Macey, H. B.: Unpublished data.

# The Lipolytic Analysis of the Duodenal Contents\*

By

BRADFORD N. CRAVER, Ph.D.

and

BURNHAM S. WALKER, M.D.

BOSTON, MASSACHUSETTS

SNELL and Comfort (1) recently expressed the thought that more cases of pancreatic insufficiency would be detected if pancreatic functional tests were generally available and more frequently used. Since the independent publication in 1910 by Eihorn (2) and Gross (3) of practical tubes for intubating the duodenum, various procedures have been published for the enzymic analysis of the duodenal contents. Most of the lipolytic methods have been titrimetric, i.e. the acid liberated from a suitable substrate after a stated period of hydrolysis was titrated with standard alkali. Such methods encounter a serious difficulty; the end-points are hard to read if the solution is well-buffered, and if it is not well-buffered the optimal pH for the lipase is not maintained. Only the method of Balls, Matlack and Tucker (4) has met this problem unequivocally, but their method is not clinically practicable.

In attempting to formulate a more clinically satisfactory lipolytic method, the authors established the following minimal criteria for the method: (A) the optimal pH and (B) the optimal temperature must be maintained during the course of the reaction; (C) inhibiting agents must be avoided and necessary activators or co-enzymes must be added; (D) operative variables in the system must be held to a minimum by the use of a fixed concentration of a suitable and evenly emulsified substrate; (E) the method of measuring the final extent of digestion must be accurate; (F) the enzyme must be protected from destructive influences in the interval between its procurement and its analysis; (G) the method must be simple, should preferably require ordinary laboratory apparatus and consume as little time as possible; (H) the method must be designed to give as true a picture as possible of what might be expected to occur in vivo. A critical review of the literature pertinent to these criteria is to be found elsewhere and for want of space will not be given here (5.) Probably the most vexing problem is whether or not bile activates lipase. Sobotka (6) reviews the work on that problem and is inclined to the conclusion that bile does activate lipase. He notes that bile does have a buffering action and a strong emulsifying action. Unfortunately, most of the work directed toward settling this problem has not eliminated these two variables in studying the possible activating effect of bile. McClure, Wetmore and Reynolds (7), who were among the few to work in a well-buffered medium with a well-emulsified substrate, reported that the addition of bile to their specimens did

not augment the lipolytic activities obtained. Weinstein and Wynne (8) and Baxter (9) reported the same result. Without attempting to settle this question it may be noted that the method described below does employ adequate buffering and a well-emulsified substrate. The addition of various activators is open to the theoretical objection that it might not represent what actually occurs in the patient's intestine.

## METHOD OF ANALYSIS

The method used is turbidimetric. Apparently Leubner (10) is the only one previously to have used that type of method in macro lipolytic analysis. However, his substrate, triolein, is not only more expensive but less agreeable to work with. He did not employ the refinement of serial dilutions. Herzfeld (11) devised a micro method which employed the method of serial dilutions with tributyrin as a substrate, but an emulsion prepared according to his directions was altogether too unstable for macro work. The following method is presented as more satisfactorily meeting the above mentioned criteria than previously published methods. A 1% tributyrin emulsion rendered permanent by the addition of one gram of Alkanol B per one hundred cc. is the substrate. Alkanol B is a DuPont product which, the manufacturers informed us, is alkyl-naphthalene sodium sulfonate. This emulsion is stable after putting it twice through a hand homogenizer and will keep at least one month in the ice box. The only other reagents required are three solutions of sodium bicarbonate: 1.00%, 1.11% and 1.25%. The method is one of serial dilution and all analyses are done in duplicate. Ten tubes, of the proper size and uniformity for use with the Evelyn Photoelectric Colorimeter, are set up in pairs to contain the following reagents: tube 1 receives 4 cc. of 1.25%  $\text{NaHCO}_3$ ; tube 2, 9 cc. of 1.11%  $\text{NaHCO}_3$ ; tubes 3, 4 and 5, 5 cc. of 1.00%  $\text{NaHCO}_3$ . To tube 1 is added 1 cc. of the duodenal specimen to be analyzed and the same to tube 2. After thorough mixing, 5 cc. of the contents of tube 2 are added to tube 3. In like manner 5 cc. of the contents of tube 3 are added to tube 4, etc. Five cc. are taken from the last tube of the series and discarded. In working with the duodenal contents a sixth tube is occasionally necessary and with experience one may predict it by noting the speed of digestion in the first tubes of the series immediately after the addition of the substrate. As soon as the various enzymic dilutions have been made, five cc. of the substrate are rapidly added to each tube. The tubes are then all well-stoppered, shaken and incubated in a water bath for two hours at 40° C. The time interval begins the moment the substrate is added to the first tube and ends the moment the first

\*Abridgement of a dissertation submitted by Bradford N. Craver to the faculty of the Graduate School of Boston University in partial fulfillment of the requirements for the degree of Doctor of Philosophy. Dr. Craver's present address is Wayne University College of Medicine, Detroit, Michigan.  
Submitted Dec. 15, 1941.

tube is read in the Evelyn Photoelectric Colorimeter. The tubes should be read in the same order in which they are filled for within narrow limits it takes as long to fill them as it takes to read them in the colorimeter and in that way slight differences in the time of digestion for each tube are held to a minimum. Filter No. 565 is used for the colorimetric readings. 95% of the light which it transmits lies in the range between 550 and 580 millimicra.

For comparative purposes single figures expressing the relative enzymic effects of each specimen were obtained in the following manner: it was assumed that each tube exhibiting complete digestion, as shown by the reading in the colorimeter and the grossly apparent clarification of the tube's contents, had present 1% of undigested substrate. By using the equation of a first order reaction and expressing the time in minutes, a value for the velocity constant of 0.03838 was obtained. This figure was multiplied by the reciprocal of the dilution of the specimen in the last tube of the series showing complete digestion and to that product was added the constant calculated from the Evelyn reading of the first tube in the series to show incomplete digestion. For clinical purposes it suffices to note the number of tubes in the series revealing complete digestion.

The percentage of digestion of the substrate indicated by the colorimetric readings is determined by interpolation on a graph which represents the curve obtained by plotting the per cent of undigested substrate against the colorimetric readings of standard dilutions of the substrate. For that purpose five tubes are prepared containing respectively 5, 4, 3, 2 and 1 cc. of the substrate diluted to a total volume, in each case, of 10 cc. with 1%  $\text{NaHCO}_3$ . In this case, as in all determinations, 10 cc. of 1%  $\text{NaHCO}_3$  serves as a blank. The readings so obtained for different lots of emulsion do not vary by more than one-quarter of a unit from the respective values: 5°, 6°, 7°, 11° and 21° where the superscripts as usual indicate quarter units.

#### REPORT OF ANALYSIS

The foregoing method was employed in the analysis of specimens obtained from fifty intubations, the results of which are recorded in Table I. The subjects comprised ten hospital patients, twelve healthy nurses and twenty-one healthy medical students, of which latter group two were women. The hospital patients had what may be termed assorted disorders but none were of the type for which this test may be considered of diagnostic value. The activity in fasting specimens was found to range from zero to complete digestion through the fifth tube and partial digestion in the sixth. The specimens obtained at varying intervals, usually fifteen minutes, after stimulation of the duodenal mucosa with twenty cc. of 0.1 N HCl displayed activity varying from complete digestion through the second tube with partial digestion in the third to complete digestion through the fifth with partial digestion in the sixth. The latter group showed a sufficiently narrow range of dispersion to permit statistical analysis on the basis of the number of tubes showing complete digestion. The 64 specimens analyzed after stimulation gave a mean of 3.34 tubes with a standard deviation of 0.82 and a probable error of

the mean of 0.07. The chance of finding normal cases showing complete digestion only through the first tube was found to be 22 in 10,000. The analogous figure for complete digestion through the sixth tube was 6 in 10,000. The same figures for the group exclusive of

TABLE I

| Case No. | Last Tube Showing Complete Digestion | % Undigested | $K=2.303 \log \frac{a}{a-x}$ |
|----------|--------------------------------------|--------------|------------------------------|
| 1-f      | 5                                    | 100*         |                              |
| 1-15     | 4                                    | 66           | .31                          |
| 2-f      | 3                                    | 19           | .17                          |
| 2-15     | 3                                    | 14           | .17                          |
| 3-f      | 3                                    | 17           | .17                          |
| 3-15     | 3                                    |              |                              |
| 4-f      | 4                                    | 93           | .31                          |
| 4-15     | 4                                    | 49           | .31                          |
| 5-f      | 4                                    | 72           | .31                          |
| 5-15     | 4                                    | 66           | .31                          |
| 6-f      | 3                                    | 25           | .17                          |
| 6-15     | 4                                    | 19           | .32                          |
| 7-f      | 3                                    | 43           | .16                          |
| 7-15     | 4                                    | 7            | .33                          |
| 8-f      | 4                                    | 13           | .32                          |
| 8-15     | 3                                    | 23           | .17                          |
| 9-f      | 3                                    | 20           | .17                          |
| 9-15     | 3                                    | 10           | .17                          |
| 10-f     | 4                                    | 45           | .31                          |
| 10-15    | 5                                    | 93           | .61                          |
| 11-f     | 5                                    | 58           | .62                          |
| 11-15    | 5                                    | 38           | .62                          |
| 12-f     | 4                                    | 11           | .33                          |
| 12-15    | 3                                    | 58           | .16                          |
| 13-f     | 3                                    | 40           | .16                          |
| 13-15    | 4                                    | 38           | .32                          |
| 14-f     | 4                                    | 11           | .33                          |
| 14-15    | 3                                    | 88           | .15                          |
| 15-f     | 4                                    | 20           | .32                          |
| 15-15    | 4                                    | 19           | .32                          |
| 16-f     | 4                                    | 12           | .32                          |
| 16-15    | 5                                    | 100*         |                              |
| 17-f     | 4                                    | 21           | .32                          |
| 17-15    | 4                                    | 9            | .33                          |
| 18-f     | 4                                    | 44           | .31                          |
| 18-15    | 4                                    | 51           | .31                          |
| 19-f     | 3                                    | 13           | .17                          |
| 19-15    | 4                                    | 44           | .31                          |
| 20-f     | 3                                    | 18           | .17                          |
| 20-15    | 4                                    | 77           | .31                          |
| 21-f     | 2                                    | 72           | .08                          |
| 21-15    | 4                                    | 73           | .31                          |
| 22-f     | 2                                    | 7            | .18                          |
| 22-15    | 2                                    | 73           | .08                          |
| 23-f     | 44                                   | 44           | .31                          |
| 23-15    | 44                                   | 40           | .31                          |
| 24-f     | 5                                    | 35           | .52                          |
| 24-15    | 4                                    | 28           | .32                          |
| 25-f     | 4                                    | 7            | .33                          |
| 25-30    | 4                                    | 14           | .32                          |
| 26-f     | 5                                    | 83           | .52                          |
| 26-15    | 4                                    | 75           | .31                          |
| 27-f     | 2                                    | 16           | .69                          |
| 27-15    | **                                   |              |                              |
| 28-f     | 1                                    | 40           | .05                          |
| 28-15    | 3                                    | 39           | .16                          |
| 29-f     | 0                                    |              |                              |
| 29-10    | 3                                    | 17           | .17                          |
| 29-20    | 3                                    | 15           |                              |
| 30-f     | 3                                    | 6            | .18                          |
| 30-15    | 3                                    | 22           | .17                          |

the ten hospital patients (all of whom, however, gave results falling within normal limits but tending to fall in the lower range of normal) were: mean, 3.80; standard deviation, 0.72; and probable error of the mean, 0.07. On the basis of this limited group the chance of finding a normal case with complete digestion only through the first tube was found to be

TABLE I (CONTINUED)

| Case No. | Last Tube Showing Complete Digestion | % Undigested | $K=2.303 \log \frac{a}{a-x}$ |
|----------|--------------------------------------|--------------|------------------------------|
| 31-f     | 3                                    | 39           | .16                          |
| 31-15    | 3                                    | 19           | .17                          |
| 32-f     | 3                                    | 17           | .17                          |
| 32-15    | 2                                    | 20           | .09                          |
| 33-f     | 1                                    | 72           | .04                          |
| 33-15    | 4                                    | 65           | .31                          |
| 34-f     | 4                                    | 10           | .33                          |
| 34-10    | 5                                    | 100*         |                              |
| 34-20    | 1                                    | 3            | .34                          |
| 35-f     | 0                                    |              |                              |
| 35-10    | 3                                    | 15           | .17                          |
| 35-20    | 3                                    | 10           | .17                          |
| 36-f     | 4                                    | 27           | .32                          |
| 36-15    | ***                                  |              |                              |
| 37-f     | 3                                    | 23           | .17                          |
| 37-10    | 2                                    | 18           | .09                          |
| 37-20    | 3                                    | 62           | .16                          |
| 38-f     | 4                                    | 38           | .32                          |
| 38-10    | 4                                    | 62           | .31                          |
| 38-20    | 2                                    | 21           | .17                          |
| 39-f     | 2                                    | 41           | .08                          |
| 39-10    | 2                                    | 34           | .09                          |
| 39-20    | 2                                    | 34           | .09                          |
| 40-f     | 4                                    | 11           | .32                          |
| 40-15    | 4                                    | 44           | .31                          |
| 40-25    | 4                                    | 19           | .32                          |
| 41-f     | 4                                    | 13           | .32                          |
| 41-15    | 4                                    | 41           | .31                          |
| 41-25    | 4                                    | 28           | .32                          |
| 42-f     | 0                                    |              |                              |
| 42-5     | 3                                    | 77           | .16                          |
| 42-10    | 3                                    | 17           | .17                          |
| 42-20    | 3                                    | 19           | .17                          |
| 43-f     | 3                                    | 68           | .16                          |
| 43-10    | 4                                    | 17           | .32                          |
| 43-20    | 2                                    | 19           | .17                          |
| 44-f     | 4                                    | 31           | .31                          |
| 44-5     | 4                                    | 51           | .31                          |
| 44-10    | 4                                    | 60           | .31                          |
| 44-20    | 4                                    | 51           | .31                          |
| 45-f     | 2                                    | 47           | .08                          |
| 45-10    | 12                                   | 39           | .08                          |
| 45-20    | 12                                   | 19           | .09                          |
| 46-f     | 12                                   | 63           | .08                          |
| 46-5     | 12                                   | 44           | .08                          |
| 46-10    | 12                                   | 73           | .08                          |
| 46-20    | 12                                   | 56           | .08                          |
| 47-f     | 12                                   | 53           | .08                          |
| 47-5     | 12                                   | 55           | .08                          |
| 47-10    | 12                                   | 55           | .08                          |
| 47-20    | 12                                   | 63           | .08                          |
| 48-f     | 2                                    | 55           | .08                          |
| 48-5     | 12                                   | 55           | .08                          |
| 48-10    | 2                                    | 52           | .08                          |
| 48-20    | 12                                   | 37           | .09                          |
| 49-f     | 3                                    | 45           | .16                          |
| 49-15    | 5                                    | 13           | .17                          |
| 50-f     | 5                                    | 100*         |                              |
| 50-10    | 5                                    | 100*         |                              |
| 50-20    | 5                                    | 100*         |                              |

† f-fasting, and second figure—number of minutes after stimulation.

\* By the end of two hours these specimens showed complete digestion through the fifth tube but a sixth could not be done because too little of the specimen remained. Experience had indicated that digestion in the sixth would have been partial because of the slow rate of digestion in the fifth.

\*\* Specimen not obtained because subject could not keep tube down.

\*\*\* Specimen acid and could not be used

TABLE II

| Subject | Case No. in Table I            | Intubation No.   | Last Tube Showing Complete Digestion |
|---------|--------------------------------|------------------|--------------------------------------|
| 1       | 1-f<br>1-15                    | 1<br>1           | 5<br>4                               |
|         | 22-f<br>22-15                  | 2<br>2           | 3<br>2                               |
| 2       | 12-f<br>12-15                  | 2<br>2           | 4<br>3                               |
|         | 27-f<br>27-15                  | 1<br>1           | 2<br>not done                        |
| 3       | 18-f<br>18-15                  | 1<br>1           | 4<br>4                               |
|         | 42-f<br>42-5<br>42-10<br>42-20 | 2<br>2<br>2<br>2 | not done<br>1<br>3<br>3              |
| 4       | 21-f<br>21-15                  | 1<br>1           | 2<br>4                               |
|         | 26-f<br>26-15                  | 2<br>2           | 5<br>4                               |
| 5       | 23-f<br>23-15                  | 1<br>1           | 1<br>4                               |
|         | 50-f<br>50-10<br>50-20         | 2<br>2<br>2      | 5<br>5<br>5                          |
| 6       | 24-f<br>24-15                  | 1<br>1           | 5<br>1                               |
|         | 34-f<br>34-10<br>34-20         | 2<br>2<br>2      | 4<br>5<br>4                          |
| 7       | 25-f<br>25-30                  | 1<br>1           | 4<br>4                               |
|         | 40-f<br>40-15<br>40-25         | 2<br>2<br>2      | 4<br>1<br>4                          |

one in 10,000 and the chance of finding a normal case revealing complete digestion through the sixth tube was found to be eleven in 10,000.

In fifteen cases at least two specimens obtained after stimulation were analyzed and in five of those, three specimens were analyzed. These results are recorded in Table II. They usually showed complete digestion through the same number of tubes but in a few of the cases differed by one tube in that respect. It was concluded, therefore, that for clinical purposes the analysis of more than one specimen obtained after stimulation was not necessary.

Seven subjects were twice intubated. Of those seven, three gave specimens after stimulation of the same strength on the two different occasions. Of the remaining four, two gave results differing by only one tube: one differed by two tubes on the two occasions; the results in the seventh case cannot be compared as a neutral or faintly alkaline specimen after stimulation was not obtained after one of the two intubations. With the subject whose specimens differed by two tubes the first intubation, which gave the lowest value, took an exceptionally long time. The results indicate a tendency for specimens obtained from the same individual on different occasions to be closely parallel in enzymic activity.

## DISCUSSION

Two points in connection with this test deserve further explanation. The first is the choice of stimulant and the second is the choice of substrate. Hydro-



chloric acid was employed because it is one of the normal physiological stimulants for setting the secretin mechanism in motion, a relationship now too well established to warrant further discussion. In clinical testing it might be desired to employ secretin (12-16) or some other stimulant to pancreatic flow. In such an event, it would be necessary to redetermine the normal output.

There are those, as Cherry and Crandall (17), who consider tributyrin an unsuitable substrate for lipase; they consider that its hydrolysis rather reflects the activity of an esterase. The work of Falk (18) indicates that even the simple triglycerides reflect the activity of pancreatic lipase rather than of its esterase. Myers, Free and Beams (19) reported that human duodenal contents gave comparable results with triolein or tributyrin as the substrate. Wolvekamp and Griffioen (20) found the esterase activity of their pancreatic extracts apparently did not account for the hydrolysis of tributyrin. Sure, Kik and Buchanan (21) discovered that tributyrin gave results more closely paralleling those obtained with olive oil than those obtained with a known substrate for esterase. The work of Bamann and Feichtner (22) strengthens the contention that tributyrin is a suitable substrate for determining the activity of a lipase.

Insofar as possible the lipolytic test herein described meets the other requirements set forth for a satisfactory clinical method of enzymic analysis. The sodium bicarbonate used is sufficient to neutralize all the butyric acid liberated from the substrate and still maintain a neutral or slightly alkaline pH.

Others have already made it abundantly clear that the enzymic analysis of the duodenal contents can have only a limited usefulness. That should not, however, preclude such analysis with patients suspected of pathological conditions upon which this analysis may shed some light. Obviously the test can do no more than direct attention to a possible pancreatic mal-

function, whether due to an endogenous or an exogenous lesion. Many workers have shown the value of a lipolytic analysis of the duodenal contents in distinguishing a pancreatogenous steatorrhea from other types of steatorrhea (15, 23-32.) The test can be of assistance in diagnosing chronic pancreatitis (14, 18, 26, 30, 33-41.) It may strengthen the clinician's suspicion of a pancreatic or vicinal malignancy provided the position of the neoplasm is such as to interfere with the delivery to the duodenum of the gland's external secretion (14, 26, 30, 36, 39, 40, 42-45). It may assist in the diagnosis of pancreatic calculi which the recent studies of Snell and Comfort (1) have indicated are not quite as rare as once thought. The test may serve to detect a mild concomitant pancreatitis in certain pathological disturbances of the liver and biliary system (14, 26, 28, 37, 41, 43, 46.)

Because of the relative scarcity of conditions to which this test is applicable, the authors hope that others may apply it to suitable cases in an effort to determine its diagnostic usefulness in the light of the normal standards herein contained.

### SUMMARY

1. A simple, clinical method of lipolytic analysis is described, applicable to duodenal contents, and employing the principle of serial dilutions with tributyrin as a substrate.

2. The results of fifty intubations on normal subjects are reported to serve as a standard of reference.

The authors wish to express their appreciation to Dr. F. Ingelfinger for his criticism of the experimental work and of the manuscript.

The authors thank those members of the class of 1944 at Boston University School of Medicine and the cooperating nurses of Massachusetts Memorial Hospital who generously volunteered as the subjects for this study.

The authors wish to thank Miss Kathryn Rakesky for technical assistance.

### REFERENCES

1. Snell, A. M. and Comfort, M. W.: The Incidence and Diagnosis of Pancreatic Lithiasis. Review of 18 cases. *Am. J. Dig. Dis.*, 8:237, 1941.
2. Einhorn, M.: Ueber Gewinnung von Duodenalinhalten beim Menschen. *Berlin. Klin. Wochschr.*, 12:522, 1910.
3. Gross, M.: A Duodenal Tube (Preliminary communication.) *N. Y. Med. J.*, 91:77, 1910.
4. Ball, A. K., Matlack, M. B. and Tucker, I. W.: The Hydrolysis of Glycerides by Crude Pancreatic Lipase. *J. Biol. Chem.*, 122:125, 1937.
5. Craver, B. N.: The Lipolytic Activity of the Duodenal Contents. Ph.D. Dissertation, Boston University, 1941.
6. Sobotta, H.: Physiological Chemistry of the Bile. Williams & Wilkins Company, Baltimore, Md., 1937.
7. McClure, C. W., Wetmore, A. S. and Reynolds, L.: New Methods of Estimating Enzymatic Activities of Duodenal Contents of Normal Men. *Arch. Int. Med.*, 27:705, 1921.
8. Weinstein, S. S. and Wynne, A. M.: Studies on Pancreatic Lipase I. *J. Biol. Chem.*, 112:641, 1935-36.
9. Baxter, S. G.: The Parallel Concentration of Enzymes in the Pancreatic Juice. *Am. J. Dig. Dis. and Nutr.*, 2:108, 1935.
10. Leubner, H.: Determination of Enzymes in the Duodenum. III. Lipase. *CA*, 33:8648, 1939; *Arch. Verdauungs-Krankh.*, 1:153.
11. Herfeld, E.: Über eine einfache Tyndallmetrische Methode zur Messung von Lipasewirkungen. *Mikrochemie*, 15:227, 1934.
12. Agren, G., Lagerlof, H. and Berglund, H.: The Secretin Test of Pancreatic Function in the Diagnosis of Pancreatic Disease. *Acta Med. Scand.*, 90:224, 1936.
13. Chiray, M., Salmon, A. R. and Mercier, Mlle. A.: Action de la Sécrétine Purifiée sur la Sécrétion Externe du Pancréas de l'Homme. (Note préliminaire.) *Bull. méd. soc. méd. hôp.*, Paris, Series 3, 50:1317, 1926.
14. Comfort, M. W.: Tests of Pancreatic Function. *J. Am. Med. Ass'n.*, 115:2044, 1940.
15. Diamond, J. S. and Siegel, S. A.: The Secretin Test in the Diagnosis of Pancreatic Diseases with a Report of One Hundred Thirty Tests. *Am. J. Dig. Dis.*, 7:435, 1940.
16. von Löffler, W.: Zur Klinik der Pankreaserkrankungen. *Arch. Verdauungs-Krankh.*, 63:249, 1938.
17. Cherry, I. S. and Crandall, L. A.: The Specificity of Pancreatic Lipase: Its Appearance in the Blood After Pancreatic Injury. *Am. J. Physiol.*, 109:256, 1932.
18. Falk, K. G.: Directive Influences in Biological Systems. III. The Effect of Proteases on Lipase Actions. *J. Biol. Chem.*, 102:553, 1933.
19. Myers, V. C., Free, A. H. and Beams, A. J.: Variations in the Enzymatic Activity of Duodenal Contents. *Am. J. Dig. Dis.*, 5:174, 1938.
20. Wolvekamp, H. P. and Griffioen, K.: Über Lipase und Esterase Wirkung des Pankreassaftes. *Z. physiol. Chem.*, 223:136, 1934.
21. Sure, E., Kik, M. C. and Buchanan, K. S.: Enzymic Efficiency in Avitaminosis. II. Influence of Vitamin B Deficiency on Efficiency of Pancreatic Lipase and Esterase. *J. Biol. Chem.*, 108:27, 1935.
22. Bamann, E. and Feichtner, C.: Autokatalytischer Anstieg der Umsatzgeschwindigkeit bei der Esterspaltung durch Pankreassaft-Lipase und seine Ursache. *Biochem. Z.*, 25:295, 1936.
23. Bondi, S. and Salomon, H.: Zur Beurteilung der Pankreassaftsekretion. *Wien. med. Wochschr.*, 63:1722, 1913.
24. Thaysen, Th.E.: On Steatorrhea. *Acta Med. Scand. Suppl.*, 15:384, 1926.
25. Norregaard, A. and Thaysen, Th.E.: Wasserstoffionkonzentration und Fermentgehalt im Duodenalsaft. *Acta Med. Scand.*, 65:15, 1928.
26. Hotz, H. W.: Zur Differentialdiagnose und Therapie der Steatorrhea. *Arch. Verdauungs-Krankh.*, 63:319, 1938.
27. Comfort, M. W., Parker, R. L. and Osterberg, A. E.: The Concentration of Pancreatic Enzymes in the Duodenum of Normal Persons and Persons with Disease of the Upper Part of the Abdomen. *Am. J. Dig. Dis.*, 6:249, 1939.
28. Gubergritz, M. M.: Zur Diagnostik der Pankreaserkrankungen. *Arch. Verdauungs-Krankh.*, 50:89, 1931.
29. Diamond, J. S., Siegel, S. A. and Gail, M. G.: The Use of Secretin as a Clinical Test of Pancreatic Function. *Am. J. Dig. Dis.*, 6:366, 1939.
30. Dubois-Ferrière, H.: Atrophic Lipomatose Dupankreas. Spätes Symptomatische. *Rev. Med. de la Suisse Rom.*, 59:738, 1939.
31. Lagerlof, H.: The Secretin Test of Pancreatic Function. *Quart. J. Med.*, 8:115, 1933.
32. Rauch, S., Litvak, A. M. and Steiner, M.: Congenital Familial

- Steatorrhea with Fibromatosis of the Pancreas and Bronchiectasis. *J. Ped.*, 14:462, 1939.
33. Epphorn, M.: Recent Studies of Pancreatic Secretion. *Med. Record*, 87:967, 1915.
  34. Chace, A. F. and Myers, V. C.: The Examination for Diagnostic Purposes of the Enzyme Activity of Duodenal Contents. *Arch. Int. Med.*, 12:628, 1915.
  35. Crohn, B. B.: The Enzymic Power of Duodenal Contents as a Means of Diagnosis of the Functional Activity of the Pancreas. *Biochem. Bull.*, 2:454, 1913.
  36. Crohn, B. B.: The Early Diagnosis of Carcinoma of the Bile and Pancreatic Ducts. *Am. J. Surg.*, 29:270, 1915.
  37. Gunk, M. and Klein, P.: Zur klinischen Verwendbarkeit der Duodenalsonde. *Med. Klin.*, 10:768, 1914.
  38. Hollander, E.: A Clinical Method for the Quantitative Determination of Pancreatic Ferments in Duodenal Contents. *J. Lab. Clin. Med.*, 16:460, 1931.
  39. Chiray, M., Lebon, J. and Gozlan, W.: Etude de l'insuffisance Pancreatique Externe par le Dosage des Enzymes dans le Suc Duodénal Prélevé par Tubare. *Bull. mémoires. Acad. Méd. Paris*, 329, 1926.

40. Berger, W.: Aus der inneren Klinik der Pankreaserkrankungen. I. Die Leichte Pankreopathie. II. Die Stellung des Pankreas im endokrinen System. *Wien. Klin. Wochschr.*, 45:1473, 1933.
41. Berger, W. and Schnetz, H.: Autoptische und Biopische Kontrollen der Pankreasfunktionsprüfungen. *Deut. Arch. Klin. Med.*, 184:1, 1935.
42. Adler, E.: Über Ergebnisse der Duodenalsondierung. *Prager med. Wochschr.*, 39:52, 1914.
43. Crohn, B.: The Diagnosis of the Functional Activity of the Pancreatic Gland by Means of Ferment Analyses of the Duodenal Contents and of the Stools. *Am. J. Med. Sci.*, 145:393, 1913.
44. Deloch, E.: Zur Funktionsprüfung der äußeren Pankreassekretion durch Untersuchung des Duodenalsaftes. *Arch. Verdauungskrankh.*, 30:27, 1922.
45. Lueders, C. W.: Quantitative Estimation of Enzyme Concentration in Duodenal Fluids. A Practical Clinical Method. *Am. J. Dig. Dis. and Nutrit.*, 2:224, 1935.
46. Isaacs-Krieger, K.: Zur Quantitativen Bestimmung der Fermente im Duodenalsaft. *Z. klin. Med.*, 92:259, 1921.

## Purpura Due to Vitamin K Deficiency in Anorexia Nervosa

By

P. M. AGGELER, M.D., S. P. LUCIA, M.D.

and

H. M. FISHBON, M.D.  
SAN FRANCISCO, CALIFORNIA

**A**BNORMAL bleeding caused by nutritional deficiency occurs in patients suffering from scurvy. In that condition the cause of the increased capillary fragility is attributed to a diminution in the amount of intercellular cement substances secondary to a deficiency in Vitamin C. It is readily cured by the administration of cevitamic acid.

In 1933 Minot (1) reported abnormal bleeding associated with a prolonged coagulation time of the blood in patients suffering from a type of chronic dietary deficiency which did not result in scurvy. The nature of the nutritional deficiency capable of altering the coagulation time of the blood was then not known.

Following the development of better methods for the determination of the prothrombin concentration of the blood (Quick, 1935 (2) and Warner, Brinkhous and Smith, 1936 (3)), it was found that marked hypoprothrombinemia could be caused by nutritional deficiency of Vitamin K secondary to obstructive jaundice, biliary fistula or diseases characterized by impaired absorptive function of the gastro-intestinal tract (4-25.) In man a slight diminution in prothrombin due solely to a deficient diet was reported by Kark and Lozner (26.) On the other hand, Scarborough (27) could not confirm this observation. Low concentrations of prothrombin due to nutritional deficiency are usually elevated to normal following the administration of Vitamin K. In patients suffering from Vitamin K deficiency, the coagulation time of the whole blood is usually prolonged when the hypoprothrombinemia is severe, and in addition, there may be defective retraction of the clot and prolongation of the bleeding time. The capillary fragility is seldom increased and the platelet count is usually normal (5.)

The present report concerns the case of a patient who suffered from anorexia nervosa associated with purpura due to Vitamin K deficiency.

### CASE REPORT

**History:** A. R., divorced white woman, age 32, first seen May 9, 1940, with complaints of anorexia, vomiting,

From the Department of Medicine, University of California Medical School, San Francisco, California.  
Submitted January 25, 1942.

diarrhea, gingival bleeding and ecchymoses. Because of anorexia associated with severe emotional maladjustments, the patient had subsisted for many years on a markedly deficient diet. Five years previously she had suffered for two months from a severe attack of anorexia, during which time she vomited all ingested food and had diarrhea (four to eight watery stools daily.) One month after the onset of anorexia, ecchymoses appeared over the entire body and persisted until the gastro-intestinal symptoms were abated. This followed readjustment of her emotional difficulties. Two years previously she had suffered from a similar attack accompanied by hemorrhage from a tooth socket and bleeding into the elbow joints. The bleeding from the tooth socket was controlled by a blood transfusion, but the purpura continued despite repeated intravenous injection of large doses of cevitamic acid. Three weeks before her present entry severe anorexia, vomiting and diarrhea had recurred. Ecchymoses had been present for five days and gingival bleeding for one day. She had taken about one pint of fresh orange juice on each of the four days preceding her entry to the clinic. She had lost eight pounds in weight.

**Physical Examination:** An agitated, poorly nourished woman appearing much older than her stated age. Weight 107 pounds. Temperature, pulse and respirations normal. The skin was pale and dry and there were many ecchymoses varying from one to four centimeters in diameter scattered over the trunk and extremities. The lymph nodes were not enlarged. The conjunctivae were normal. The pupils were equal, round and regular, and reacted to light and in accommodation. Extra ocular movements were normal. The fundi appeared normal. The tongue was not unusual. The gingival margins were spongy and bleeding. There were no evidences of cheilosis. The thyroid gland was not enlarged. The breasts were small, flat and atrophic. The heart and lungs were normal. The blood pressure was 110 mm. Hg. systolic and 70 mm. Hg. diastolic. The abdomen was scaphoid, none of the abdominal organs were palpably enlarged, and there was no tenderness or rigidity. No abnormalities were found in the pelvic and rectal examinations. The back and extremities were normal. The fundi appeared normal. The tongue was not There was no edema. The neurological examination was normal except for hyperactive deep reflexes.

**Laboratory Examination:** Gastric analysis showed low free acidity. Roentgenologic examination of the entire

gastro-intestinal tract was normal except for hypermotility of the stomach.

Blood count: Hemoglobin 104%, R.B.C. 5,400,000, W.B.C. 7,200. Diff.: PMN 64% (F. 52%, N.F. 12%), P.M.E. 2%, Lymph 29%, Mono. 5%.

Serum protein: Total 4.9 gms. %, albumen 2.65 gms. %, globulin 2.25 gms. %. (Normal range: Total 6.5-8.2 gm. %, albumen 4.6-6.7 gms. %, globulin 1.2-2.3 gms. %.)

Plasma Cevitamic acid: 0.22 mg. %. (Normal range 0.6-2.0 mg. %.)

Plasma Fibrinogen: 0.94%.

resulting in defective absorption. It is obvious that our patient did not have scurvy since the capillary fragility was normal, despite the fact that the plasma cevitamic acid level was low. Furthermore the tendency to bleed was not controlled by the administration of large quantities of fresh orange juice or the intravenous injection of large doses of cevitamic acid. The purpura was apparently due to a severe degree of hypoprothrombinemia and was cured by the administration of Vitamin K. We are unable to account for

|                                   | 5/9/40  | 5/10/40   | 5/11/40  | 5/12/40   | 5/16/40 |
|-----------------------------------|---------|---|----------|---|---------|
| Bleeding time (Ivy)               | 3 min.  | 2½ min.   | 2 min.   | 2½ min.   | 2 min.  |
| Coagulation time (Lee and White)  | 38 min. | 46 min.   | 13½ min. | 15½ min.  | 7½ min. |
| Prothrombin concentration (Quick) | 15%     | 10%   | 55%      | 60%   | 65%     |
| Clot retraction                   | Fair    | Fair  | Good     | Good  | Good    |
| Platelet count (Rees and Ecker)   | 370,000 | 390,000   | 350,000  | 340,000   | 350,000 |
| Capillary permeability (Duke)     | Normal  | Normal  | Normal   | Normal  | Normal  |
| Treatment:                        |         | 5 mc. 4-amino-2-methyl naphthol HCl intravenously |          | 3.6 mc. 2-methyl-1,4 naphthoquinone orally daily. |         |

*Course:* Bleeding and clotting tests revealed severe hypoprothrombinemia and a markedly prolonged coagulation time. The bleeding time, platelet count and capillary fragility were normal, and the clot retraction was only slightly impaired. The patient was given 5 mgms. of 4-amino-2-methyl naphthol hydrochloride\* (synthetic Vitamin K) intravenously, followed two days later by daily oral administration of 3.6 mgm. 2-methyl-1,4-naphthoquinone. The gingival bleeding ceased immediately, and the prothrombin concentration and coagulation time returned to normal (see table.) Within one week all ecchymoses had disappeared. The patient experienced, in addition, a remarkably favorable psychic effect. She became quite cheerful, vomiting and diarrhea ceased and she resumed a reasonably normal diet. In June and October of 1940 and in March of 1941 she was again seen, complaining of recurrences of vomiting and diarrhea. These attacks were of short duration and were not accompanied by purpura. The prothrombin concentrations remained normal.

### DISCUSSION

There is a twofold mechanism for the production of vitamin deficiencies in patients suffering from anorexia nervosa, one, the exogenous dietary deficiency, the other, hypermotility of the gastro-intestinal tract

the production of such a marked degree of Vitamin K deficiency in the absence of any overt evidence of other vitamin deficiencies. However, it is possible that manifestations of other vitamin deficiencies may have been prevented by the previous administration, in concentrated dosage, of the necessary vitamin substances.

Gastro-intestinal diseases in which a prothrombin deficiency has been reported include chronic ulcerative colitis, regional enteritis, chronic intestinal obstruction, sprue, idiopathic steatorrhea and various types of fistulae and surgical anastomoses. We have been unable to find any reference in the literature to severe hypoprothrombinemia caused by a purely "functional" disturbance of the gastro-intestinal tract, such as was present in this patient. On the other hand, we have found the prothrombin concentration in two other patients suffering from anorexia nervosa to be normal.

### SUMMARY

A case is presented of purpura due to hypoprothrombinemia in a patient suffering from anorexia nervosa. The abnormal bleeding state was cured by the administration of Vitamin K.

### REFERENCES

1. Minot, G. R.: Three Cases of Chronic Dietary Deficiency. *Med. Clin. No. Amer.*, 16:761, 1933.
2. Quick, A. J., Stanley-Brown, M. and Bancroft, F. W.: Study of Coagulation Defect in Hemophilia and Jaundice. *Am. J. Med. Sci.*, 199:591, 1925.
3. Warner, E. D., Brinkhaus, K. M. and Smith, H. P.: Quantitative Study on Blood Clotting: Prothrombin Fluctuations Under Experimental Conditions. *Am. J. Physiol.*, 114:667, 1936.
4. Aggeler, P. M., Lucia, S. P. and Goldman, L.: Effect of Synthetic Vitamin K Compounds on the Prothrombin Concentration in Man. *Proc. Soc. Exper. Biol. and Med.*, 43:689, 1940.
5. Aggeler, P. M. and Lucia, S. P.: The Bleeding Tendency in Diseases of the Liver and Biliary Passages. *Acta Med. Scand.*, 107: fasc. III-V, 1941.
6. Lucia, S. P. and Aggeler, P. M.: The Influence of Liver Damage on the Plasma Prothrombin Concentration and Response to Vitamin K. *Am. J. Med. Sci.*, 201:326, 1941.
7. Sweet, N. J., Lucia, S. P. and Aggeler, P. M.: A Clinico-Pathological Correlation Between Hepatic Damage and the Plasma Prothrombin Concentration. *Am. J. Med. Sci.*, 203:665, 1942.
8. Warner, E. D., Brinkhaus, K. M. and Smith, H. P.: Bleeding Tendency in Obstructive Jaundice: Prothrombin Deficiency and Dietary Factors. *Proc. Soc. Exper. Biol. and Med.*, 37:628, 1933.
9. Brinkhaus, K. M., Smith, H. P. and Warner, E. D.: Prothrombin Deficiency and the Bleeding Tendency in Obstructive Jaundice and in Biliary Fistula. *Am. J. Med. Sci.*, 196:50, 1938.
10. Butt, H. R., Snell, A. M. and Osterberg, A. E.: Phylloquinone, Its Therapeutic Effect in the Treatment of Hypoprothrombinemia.

\*Made available through the courtesy of Parke-Davis and Company, Detroit, Michigan.

- Associated with Jaundice: A Preliminary Report. Proc. Staff Meet. Mayo Clinic, 14:497, 1939.
11. Butt, H. R., Snell, A. M. and Osterberg, A. E.: Pre-Operative and Post-Operative Administration of Vitamin K. *J. A. M. A.*, 113:383, 1939.
  12. Clark, R. L., Jr., Dixon, C. T., Butt, H. R. and Snell, A. M.: Deficiency of Prothrombin Associated with Various Intestinal Disorders: Its Treatment with Antihemorrhagic Vitamin (Vitamin K). Proc. Staff Meet. Mayo Clinic, 14:407, 1939.
  13. Weir, J. F., Butt, H. R. and Snell, A. M.: Further Observations on the Clinical Use of Vitamin K. *Am. J. Dig. Dis.*, 7:485, 1940.
  14. Rhoads, J. E.: The Relation of Vitamin K to Hemorrhagic Tendency in Obstructive Jaundice, with a Report on Cerophyl as a Source of Vitamin K. *Surgery*, 5:794, 1939.
  15. Rhoads, J. E. and Fliegelmann, M. T.: The Use of 2-methyl-1,4-naphthoquinone (a Synthetic Vitamin K Substitute). *J. A. M. A.*, 114:400, 1940.
  16. Stewart, J. D. and Rourke, G. M.: Control of Prothrombin Deficiency in Obstructive Jaundice by Use of Vitamin K. *J. A. M. A.*, 113:223, 1939.
  17. Stewart, J. D.: Prothrombin Deficiency and the Effect of Vitamin K in Obstructive Jaundice and Biliary Fistula. *Ann. Surg.*, 109:558, 1939.
  18. Stewart, J. D., Rourke, G. M. and Allen, A. W.: Control of Post-Operative Bleeding in Obstructive Jaundice. *Ann. Surg.*, 110:693, 1939.
  19. Stewart, J. D. and Rourke, G. M.: Prothrombin and Vitamin K Therapy. *New England J. Med.*, 221:403, 1939.
  20. Pohle, F. J. and Stewart, J. K.: Observations on the Plasma Prothrombin and the Effect of Vitamin K in Patients with Liver or Biliary Tract Disease. *J. Clin. Invest.*, 19:365, 1940.
  21. Dinn, H. and Glavind, J.: Vitamin K in Human Pathology. *Lancet*, 1:720, 1938.
  22. Illingworth, C. F. W.: Hemorrhage in Jaundice. *Lancet*, 1:1031, 1939.
  23. Engel, R.: Sprue und Vitamin-K-Mangel. *Med. Welt.*, 13:120, 1939.
  24. Meeke, T. T.: Vitamin K Deficiency in the Absence of Jaundice. *N. Y. State J. Med.*, 40:987, 1940.
  25. Albright, F. and Stewart, J. D.: Hypovitaminosis of All Fat-Soluble Vitamins Due to Steatorrhea. Report of Case. *New Eng. J. Med.*, 223:239, 1940.
  26. Kark, R. and Lozner, E. L.: Nutritional Deficiency of Vitamin K in Man. *Lancet*, 2:1162, 1939.
  27. Scribner, H.: Nutritional Deficiency of Vitamin K in Man. *Lancet*, 1:1080, 1940.

## The Use of Sulfaguanidine in Non-Specific Ulcerative Colitis and Other Infections of the Bowel

By

JOSEPH B. KIRSNER, M.D., Ph.D., ENID C. RODANICHE, Ph.D.

and

WALTER LINCOLN PALMER, M.D., Ph.D.

CHICAGO, ILLINOIS

### INTRODUCTION

**R**ECENT studies by Marshall and his coworkers (1) have suggested that sulfaguanidine may be useful in the treatment of infections originating in or confined to the intestinal tract. This compound was found to be fairly soluble in water, poorly absorbed from the bowel, and to reduce the number of coliform bacteria in the feces of mice. Preliminary observations by Marshall et al (2) and by Lyon (3) indicate that sulfaguanidine is of definite value in the early stages of acute bacillary dysentery. Sulfaguanidine has also been used successfully in the prophylaxis of infection following resection of the large bowel (4.) Therapeutic failures have been noted in a few instances of non-specific ulcerative colitis (5), chronic bacillary dysentery (2), and typhoid fever (2.) Our experience with this drug in a series of 20 patients is herein reported to enable further evaluation of sulfaguanidine as a chemotherapeutic agent.

### METHOD OF STUDY

The series is composed of twelve patients with non-specific ulcerative colitis, two with lymphogranuloma venereum of the rectum, and two with bacillary dysentery, all of whom were studied at the Albert Merritt Billings Hospital; four additional patients with miscellaneous infections of the bowel were observed at St. Luke's Hospital. The sulfaguanidine<sup>\*</sup> was administered in conjunction with the usual therapy employed in each case. The quantity of the drug used and the duration of treatment varied as noted in the individual case reports. The smallest amount given was 37.5 gms. in 10 days to a 2 year

old infant with ulcerative colitis. The largest quantity administered was 1,132 gms. in 56 days to a 21 year old male with ulcerative colitis. In the majority of cases, 10 to 15 gms. of the drug were given daily in divided doses for a period of two to four weeks.

The investigative procedures in each case included examination of the feces for parasites, anaerobic culture of the stools for *Bacterium Necrophorum* (6), routine agglutination tests, the Frei reaction, and proctoscopic examination of the rectum and sigmoid. In addition, the following data was obtained every three to four days prior to and during chemotherapy; red and white blood cell counts, hemoglobin, differential smears, examination of the urine, and the concentration of free and total sulfaguanidine in the blood. Chemical analyses of the crystals obtained from 24 hour collections of urine in several cases were carried out at the Lederle Laboratories through the courtesy of Dr. David A. Bryce.

In fourteen of the sixteen patients studied at Billings Hospital, bacterial counts of the feces were made frequently before and during the administration of sulfaguanidine; the control period varied from 2 to 32 days. The procedure employed was as follows:

One gram of freshly passed feces was suspended in 9 cc. of sterile distilled water and shaken well with glass beads. Appropriate serial dilutions to 1-1,000,000,000 were prepared from which pour plates were made using both veal infusion and eosin methylene-blue agar. The latter media was employed to enable a more rapid evaluation of the lactose-fermenting organisms present. The plates were incubated at 37.5 degrees C. and the number of colonies per plate were counted. The total count was always made from the veal infusion agar plates since this media permits the growth of the more fastidious organisms. Typical colonies were stained and examined. In some instances further identification by special tests was carried out.

<sup>\*</sup>From the Department of Medicine, Frank Billings Medical Clinic, the University of Chicago, Chicago, Illinois.

Read before the Central Society for Clinical Research, November 8, 1941, and the Chicago Society of Internal Medicine, November 24, 1941.

<sup>\*</sup>The sulfaguanidine was supplied in generous quantities by Dr. David A. Bryce, of the Lederle Laboratories, Pearl River, N. Y.

Submitted January 25, 1942.

TABLE I

*Concentration of free and total sulfaguanidine in the blood (17 patients)*

| Case     | Amount of Sulfaguanidine | Maximum Level (mg. %) |       |
|----------|--------------------------|-----------------------|-------|
|          |                          | Free                  | Total |
| A. N.    | 37.5 gms. in 10 days     | *                     | 2.4   |
| L. C.    | 60.0 gms. in 10 days     | 1.3                   | 1.8   |
| P. M.    | 108.0 gms. in 11 days    | 2.0                   | 4.3   |
| F. T.    | 112.0 gms. in 11 days    | 2.9                   | 4.2   |
| L. P.    | 118.0 gms. in 12 days    | 3.3                   | 4.2   |
| C. H. B. | 122.0 gms. in 13 days    | 3.7                   | 4.5   |
| L. M.    | 152.0 gms. in 10 days    | 1.9                   | 2.2   |
| J. C.    | 155.0 gms. in 14 days    | 5.2                   | 5.4   |
| R. N.    | 220.0 gms. in 17 days    | —                     | 5.1   |
| M. R.    | 230.0 gms. in 16 days    | —                     | 5.0   |
| B. R.    | 256.0 gms. in 34 days    | 4.0                   | 5.5   |
| S. D.    | 280.0 gms. in 21 days    | —                     | 6.5   |
| I. D.    | 292.0 gms. in 29 days    | 5.0                   | 6.1   |
| M. C.    | 410.0 gms. in 28 days    | 9.2                   | 10.8  |
| G. R.    | 844.0 gms. in 90 days    | 6.8                   | 8.0   |
| J. F.    | 980.0 gms. in 66 days    | 9.2                   | 10.3  |
| B. A.    | 1132.0 gms. in 56 days   | 7.1                   | 8.4   |

The values are presented as so many colonies per gram of feces. The concentration of sulfaguanidine in the feces was determined in two patients using the method elaborated by Marshall et al (2.)

### RESULTS

#### (A) Concentration of Sulfaguanidine in the Blood and Feces.

The maximum concentrations of free and total sulfaguanidine in the blood are recorded in Table I. It will be noted that the levels were comparatively low

in 13 of the 17 cases for whom data are available. This finding is in agreement with previous observations. Marshall (2) obtained average values for free sulfaguanidine in the blood of only 1.9 to 3.3 mg. % and values for total blood sulfaguanidine of 2.5 to 4.5 mg. % in a series of children and adults given varying quantities of the drug. Firor and Jonas (4) reported blood levels between 2 and 4 mg. % while Corwin (9) found that the blood concentration in dogs receiving large quantities of sulfaguanidine rarely exceeded 4 mg. %. However, in three patients of the present series the free sulfaguanidine rose to levels of 7.1, 9.2 and 9.2 mg. % and the total sulfaguanidine increased to 8.4, 10.3 and 10.8 mg. % respectively indicating that considerable absorption of the drug can occur during its prolonged administration in large quantities. The concentration of sulfaguanidine in the feces in cases M. C. and B. A. measured 4200 and 2800 mg. % respectively. Similar concentrations have been reported by Marshall and his associates (2.)

#### (B) Bacterial Counts of the Feces.

These counts in the fourteen patients who were studied in detail are recorded in Table II. It will be noted that the control values varied in the same patient as well as from one case to another. Usually from 3 to 18 days of chemotherapy elapsed before any appreciable change in the counts was noted. In no instance was a sterilization of the bowel accomplished. A significant decrease in the total count with a corresponding change in the flora from gram-negative bacilli to mainly gram positive cocci occurred in six patients. The bacterial content of the feces decreased in three cases but the flora was unchanged. In general, the larger the daily intake of sulfaguanidine the more frequently was there a decrease in the bacterial counts. In four patients the bacterial flora was altered but the total count was unchanged. In the remaining patient (L. C.) no alteration occurred either in the predominant type of organism or in the bacterial

TABLE II

*Bacterial counts of feces before and during use of sulfaguanidine (14 patients)*

| Case     | Amount               | Before                    |          | During                    |          | Decrease in Count |
|----------|----------------------|---------------------------|----------|---------------------------|----------|-------------------|
|          |                      | Million Colonies Per Gram | Type     | Million Colonies Per Gram | Type     |                   |
| A. N.    | 37.5 gms. in 10 days | 6200-3800                 | Coliform | 2900-5100                 | G-cocci  | +                 |
| L. C.    | 60 gms. in 10 days   | 101- 208                  | Coliform | 104- 185                  | Coliform | 0                 |
| P. M.    | 108 gms. in 11 days  | 6- 40                     | Coliform | 6- 131                    | G-cocci  | 0                 |
| F. T.    | 112 gms. in 11 days  | 1000-1700                 | Coliform | 0.2- 0.7                  | Coliform | ++++              |
| L. P.    | 118 gms. in 12 days  | 2200-4040                 | Coliform | 1420-1760                 | G-cocci  | ++                |
| C. H. B. | 122 gms. in 13 days  | 1000-1300                 | Coliform | 219                       | G-cocci  | +++               |
| L. M.    | 152 gms. in 10 days  | 870-6000                  | Coliform | 110- 600                  | Coliform | +++               |
| J. C.    | 155 gms. in 14 days  | 390- 530                  | Coliform | 90- 477                   | G-cocci  | +                 |
| B. R.    | 256 gms. in 34 days  | 1020-1040                 | Coliform | 5- 9                      | G-cocci  | +++++             |
| I. D.    | 292 gms. in 29 days  | 460- 750                  | Coliform | 4- 9                      | G-cocci  | +++++             |
| M. C.    | 410 gms. in 28 days  | 500-1080                  | Coliform | 13- 95                    | G-cocci  | +++++             |
| G. R.    | 844 gms. in 90 days  | 20- 52                    | Coliform | 0.2- 0.9                  | G-cocci  | +++++             |
| J. F.    | 980 gms. in 66 days  | 800-13,500                | Coliform | 0.3- 80                   | G-cocci  | +++++             |
| B. A.    | 1132 gms. in 56 days | 325- 490                  | Coliform | 102- 706                  | Coliform | +++               |

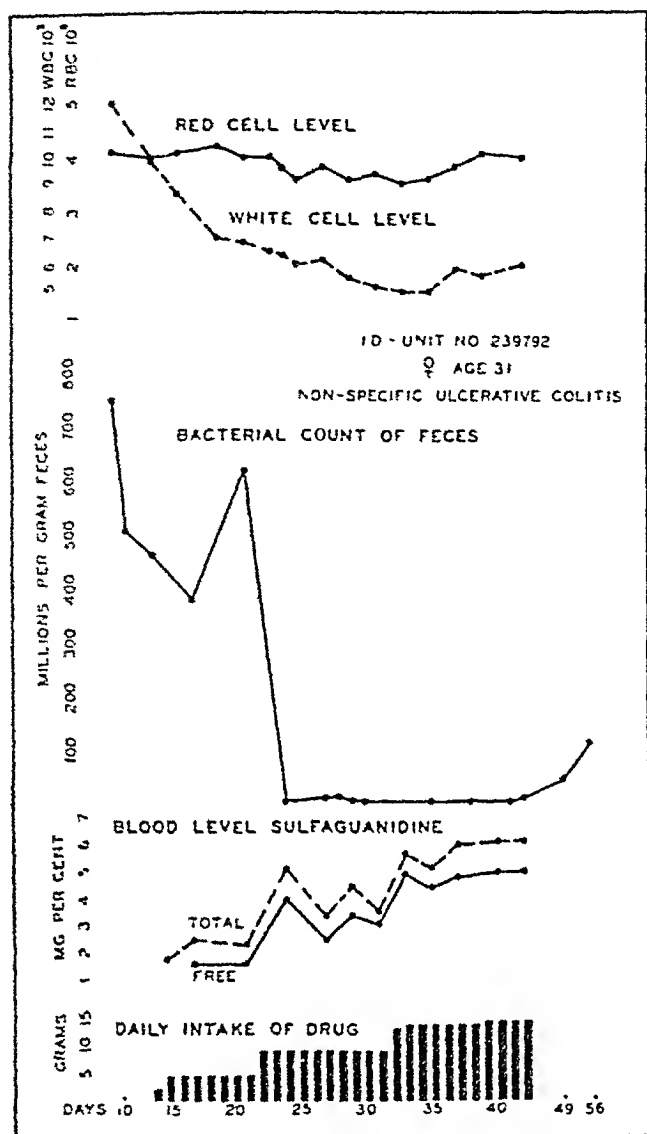


Fig. 1

count. The coliform bacteria in some instances were completely eliminated from the stools and did not appear even when plates were streaked directly from the fecal mass. In other instances, the coliform bacteria persisted in the highest concentrations but were not present in the highest dilutions. The predominant organism after the institution of chemotherapy usually was the green streptococcus, but staphylococci, gram-positive, spore-bearing bacilli, yeasts, and moulds also were present.

Bacterial counts made in several cases after the termination of treatment revealed a rapid increase of the coliform bacteria with a corresponding rise in the total count. Although too little of the drug was carried over in the dilutions employed to exert any possible bacteriostatic effect, it was considered of interest to ascertain whether para-amino-benzoic acid in vitro might counteract the effect of sulfaguanidine as it does with sulfanilamide. For this purpose, para-amino-benzoic acid was added to the various fecal dilutions in two instances; no alteration was produced thereby in the total count or in the relative proportion of the different bacterial types. Black et al (7) and MacKenzie et al (8) have reported, on the other hand, that para-amino-benzoic acid in vivo prevented the

growth-inhibiting effect of sulfaguanidine in rats fed a purified ration.

The present findings are consistent with previously reported data. The most extreme change noted by Firor and Jonas was a decrease from 16,720,000 to 10,000 colonies after 14 days of chemotherapy. Corwin (9) found, on the other hand, that the administration of sulfaguanidine in dogs and monkeys did not produce a decrease in the total number of organisms in the feces; the gram positive bacteria, particularly the cocci, increased at the expense of the gram negative bacilli. This reversal of bacterial predominance occurred almost immediately and in some instances the gram negative bacilli apparently disappeared completely. Firor and Poth (10) observed a more frequent reduction in the number of coliform bacteria in the stool when the drug was given at frequent intervals throughout the day rather than in several large doses. Bornstein and Strauss (11) have shown that sulfaguanidine also is effective against *S. cholerae* suis and to some extent against *S. paratyphi* A, but is ineffective against other organisms of the *Salmonella* group.

#### (C) Toxicity.

Few toxic reactions have been observed during sulfaguanidine therapy. A moderate decrease in the hemoglobin (not definitely attributable to the medication) was noted in three of 25 children given therapeutic doses of the drug (2); there was no hematuria, no effect apparent on the leukocyte count, no rashes, and no drug fever. In 25 adults receiving the drug for a variety of conditions, toxic reactions occurred or were suspected in three cases (2); (a) drug fever and unilateral conjunctivitis on the second day; (b)

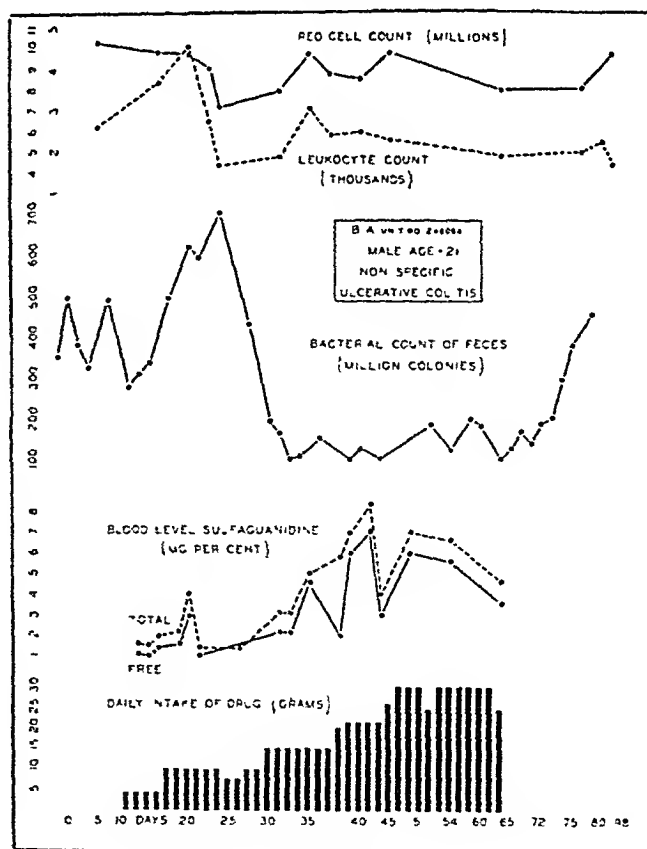


Fig. 2



possible mild leukocytic anemia on the third day, and (c) fever on the eighth day. No harmful effects have been reported by Lyon, and by Firor and Jonas. Firor and Poth (10) believe that while it is possible to reduce regularly the concentration of coliform organisms in the intestine, this cannot always be accomplished without the occurrence of high blood levels of the drug or the appearance of toxic symptoms. Mild toxic manifestations were noted by them in four of thirty-six patients receiving the drug. Corwin (9) found that "under ordinary conditions, any animal which absorbs sulfaguanidine poorly and does not acetylate it to excess, as the monkey, can ingest the drug over a relatively long period of time, at least four weeks, without ill effects."

Toxic reactions during the use of sulfaguanidine were observed in four patients of the present series. In case J. C. on the eleventh day of chemotherapy, after 131 gms. of the drug had been given, the blood smear contained a considerable number of toxic metamyelocytes such as are seen in agranulocytic reactions. During the next 48 hours these changes became more pronounced and all the cells of the polymorph series were toxic metamyelocytes. Coincident with this finding there appeared a partly scarlatini-form, partly morbilliform generalized skin eruption. The sulfaguanidine was discontinued and the dermatitis and toxic blood cells promptly disappeared.

In case G. R., after 106 gms. of the drug had been administered in 11 days, an erythematous, papular eruption appeared on the outer surfaces of both upper arms, associated with a generalized urticaria. The dermatitis subsided rapidly upon the discontinuation of the sulfaguanidine. This patient subsequently received more than 700 gms. of the drug without toxic manifestations.

In case F. T., a diffuse, erythematous, papular eruption appeared after 102 gms. of sulfaguanidine had been administered in 10 days. The dermatitis subsided rapidly after discontinuation of chemotherapy. Three days later when 2 gms. of the drug had been given, a similar rash quickly appeared, preventing the resumption of sulfaguanidine treatment.

In case L. M., after 92 gms. of the drug had been administered in 6 days, a symmetrical vesicular eruption, resembling erythema multiforme, appeared on the face. The dermatitis persisted for four additional days of continued chemotherapy but rapidly disappeared when the sulfaguanidine was discontinued.

In case A. N. there was one day of unexplained fever which subsided in 24 hours despite the continuation of therapy. In several cases there was an appreciable drop in the red blood cell counts. The leukocyte count frequently diminished to levels between 4000 and 5000 but, with the one exception noted previously, toxic granulopenia was not observed. The urine remained normal in every instance. Varying quantities of crystalline N<sub>2</sub>-acetylsulfanilylguanidine were found in the urine in those cases in which it was sought for. There was no nausea or vomiting. Despite the reactions described above, sulfaguanidine appeared to be less toxic than other commonly used sulfonamides. The low toxicity of sulfaguanidine is well

illustrated in patient B. A., who received 1,132 gms. of the drug without deleterious effects.

#### (D) Clinical Results.

##### 1. Non-Specific Ulcerative Colitis.

Sulfaguanidine in varying dosage was administered to twelve patients with non-specific ulcerative colitis. The disease was arbitrarily classified as mild in one, moderately severe in five, and severe in six patients; one of this last group progressing to a fatal termination. In six patients clinical improvement had already taken place prior to chemotherapy and the drug was given primarily to study its effect upon the fecal flora. The clinical course in these six cases was unchanged in three and slightly improved in three. The following case report is a representative example of this group:

Case B. A. (Unit No. 240084) Fig. 2. A 21-year old male college student with a chronic nonspecific ulcerative colitis of 8 months' duration was admitted to the hospital acutely ill as a result of a severe exacerbation of symptoms. He was markedly dehydrated; there was tenderness and muscle rigidity over the lower abdomen. Examination of the stools for parasites, routine agglutination tests, and the Frei reaction were negative. Bacterium *Necrophorum* was isolated from anaerobic cultures of the stool. The rectal mucosa on proctoscopy examination was edematous, friable, and bled easily. The patient remained critically ill for several weeks; his temperature fluctuated between 99 and 104 degrees and the number of stools varied from 6 to 21 per day. Sulfanilamide in doses of 5.4 grams daily was given between the 14th and 20th hospital days without noticeable improvement. Treatment also included the use of sedatives, vitamins, and blood transfusions. The patient improved gradually during the next two months, although his temperature continued to be intermittently elevated. Sulfaguanidine therapy was started on the 60th hospital day and continued for 56 days; the daily dose was increased gradually from 4.8 to 9.6 grams, then to 15 grams, and finally to 30 grams daily; a total of 1,132.0 grams of sulfaguanidine was administered. There were no toxic symptoms or manifestations. The temperature returned to normal within 14 days. The number of stools decreased from 5 to 11 per day to 1 to 4 daily. The patient's body weight, which had decreased from 59.2 to 44.4 kg. during the acute phase of the illness, steadily increased to 56.2 kg. The rectal mucosa improved slightly; the edema and friability noted at the earlier examinations disappeared but the polypoid appearance and the bleeding persisted. There was no significant decrease in the red cell count directly attributable to the chemotherapy. The leukocyte count varied from 10,200 to 4,800. A few white cells were noted in the urine on several occasions but no other abnormal findings were observed except for the presence of crystalline N<sub>2</sub>-acetylsulfanilylguanidine. Renal function, as determined by the urea clearance test, remained normal. The level of free sulfaguanidine in the blood increased from 1.0 to 7.1 mg. % and the total blood sulfaguanidine from 1.5 to 8.4 mg. %. There was a definite but possibly not significant decrease in the bacterial count of the feces. The control counts varied from 325 to 490 million colonies per gram while during sulfaguanidine therapy the values usually ranged from 108 to 201 million colonies per gram. The predominant organisms were gram negative bacilli of the colon group. The discontinuation of chemotherapy was followed by a steady increase in the bacterial content of the feces.

Comment: The clinical improvement noted in this patient occurred prior to the sulfaguanidine therapy.

No beneficial results were observed during sulfaguanidine therapy in five of the remaining six cases

with non-specific ulcerative colitis. Clinical improvement was noted, however, in one patient:

Case E. F. (Unit No. 217708.) A 32 year-old female textile chemist was admitted to the hospital with a history of intermittent diarrhea of two years' duration. The stools were watery and contained blood. Proctoscopic examination revealed a markedly granular mucosa which bled after cotton wiping. Routine agglutination tests, examination of the stools for parasites and the Frei test were negative. *Bacterium neorophorum* was isolated from anaerobic cultures of the feces. Roentgen studies revealed an advanced subacute stage of ulcerative colitis involving the entire colon and terminal ileum with multiple undermined ulcers in the ascending and transverse portions of the bowel. The patient remained in the hospital for five months and improved somewhat under a program of therapy comprising the use of a low residue, non-laxative diet, tincture of belladonna, and sedatives. The number of stools per day varied from 2 to 11 with an average of 6 movements; they were loose and contained varying amounts of blood. The patient subsequently was observed in the Out-Patient Clinic for two years. During this period there was no significant change in her condition. The number of stools per day ranged from 5 to 12; the rectal mucosa continued to appear granular although the contact bleeding had subsided. At this time, two years after her discharge from the hospital and four years after the onset of illness, the patient was given 10 grams of sulfaguanidine daily. After 14 days of chemotherapy, the patient stated that she felt better than at any time during her illness; the stools were still loose but their frequency had diminished to 1 to 2 daily. After 21 additional days of sulfaguanidine therapy the stools numbered only one daily; the granularity of the rectal mucosa had disappeared and the only evidence of previous inflammation was scarring of the mucosa.

It would appear from this study that sulfaguanidine is of no particular value in the management of non-specific ulcerative colitis. Since it is possible, however, that related "sulfa" compounds may prove beneficial in this disease, the continued trial of these drugs in the treatment of non-specific ulcerative colitis seems justified.

## 2. *Lymphogranuloma Venereum*.

Sulfaguanidine was ineffective in one patient with lymphogranuloma venereum complicated by pulmonary tuberculosis. It should be pointed out that the drug was not administered for a sufficiently long period of time to permit a conclusive appraisal of its efficacy. In the second case, chemotherapy was of definite, though not curative value, the clinical improvement being associated with a marked decrease in the bacterial count of the feces. This finding is in accord with the recent experimental observations of Rodan-

iche (12.) Sulfaguanidine, however, does not appear to have any advantage over other sulfonamides in the treatment of this condition.

## 3. *Miscellaneous Infections of the Gastro-Intestinal Tract*.

Chemotherapy was of slight, temporary value in one patient with a chronic *Shigella Paradyenteria Flexner* infection, and in a second individual with a fever possibly arising in a bowel infection. It was of no benefit in one patient with a Paratyphoid B infection and in another case with an infection of the biliary tract.

The present findings indicate that sulfaguanidine, when given in moderate amounts, is absorbed to a much less degree than are other sulfonamides. Considerable absorption of the drug does occur, however, after its prolonged use in large quantities. Sulfaguanidine exerts a variable effect on the aerobic bacterial flora of the intestine. In many instances, the number of coliform bacteria is markedly reduced resulting in a predominance of the gram positive cocci. In other cases, there is no appreciable change in the bacterial count or flora. The explanation for this variable effect is not apparent at present. Our observations, in agreement with previous studies, indicate that sulfaguanidine is less toxic than other commonly used sulfonamides. This property has been attributed by Richardson (13) to the poor absorption of the drug from the bowel and by Firor and Poth to its prompt elimination by the kidneys.

## CONCLUSIONS

1. Sulfaguanidine, while not as readily absorbed from the intestine as other sulfonamides, is, nevertheless, absorbed to some extent. When doses of 10 to 15 grams are given daily, the blood levels may reach 10 mg. %.
2. Although reactions may occur during its administration, sulfaguanidine appears to be less toxic than other commonly used sulfonamides.
3. Sulfaguanidine, in doses of 10 to 15 grams daily, usually decreases the bacterial count of the feces markedly and transforms the flora from one predominantly coliform in type to one composed almost entirely of gram positive organisms.
4. Sulfaguanidine is of no value in the treatment of Paratyphoid B infection. It apparently has no advantage over other sulfonamides in the treatment of lymphogranuloma venereum. The long continued use of sulfaguanidine in chronic, non specific ulcerative colitis has not yielded any striking therapeutic results.

## REFERENCES

1. Marshall, E. K., Jr., Bratton, A. C., White, H. J. and Litchfield, J. T., Jr.: Sulfanilylguanidine: A Chemotherapeutic Agent for Intestinal Infections. *Bull. Johns Hopkins Hospital*, 67:163, 1940.
2. Marshall, E. K., Jr., Bratton, A. C., Edwards, Lydia B. and Walker, Ethel: Sulfanilylguanidine in the Treatment of Acute Bacillary Dysentery in Children. *Bull. Johns Hopkins Hospital*, 68:94, 1941.
3. Lyon, G. M.: Chemotherapy in Acute Bacillary Dysentery: II. Clinical Use. *Virginia Med. J.*, 37:54, 1941.
4. Firor, W. M. and Jonas, A. F.: The Use of Sulfaguanidine in Surgical Patients. *Ann. Surg.*, 114:19, 1941.
5. Stone, H. B., Shipley, A. M. and Brady, L.: Individual Discussions of Paper by Firor and Jonas. *Surgery*, 9:317-318, Feb., 1941.
6. Stone, H. B.: Discussion of paper, Mortality Factors in Surgical Treatment of Ulcerative Colitis. *Cave, H. W. and Thompson, J. E.: Ann. Surg.*, 114:46, 1941.
7. Dack, G. M., Kirsner, J. B., Dragstedt, L. R. and Johnson, R.: A Study of Bacterial Neorophorum in Chronic Ulcerative Colitis and of the Effect of Sulfanilamide in Treatment. *Am. J. Dig. Dis.*, 6:305, 1939.
8. Black, S., McKibbin, J. M. and Elrehjem, C. A.: Use of Sulfaguanidine in Nutrition Experiments. *Proc. Soc. Exper. Biol. and Med.*, 47:308, 1941.
9. MacKenzie, J. B., MacKenzie, C. G. and McCollum, E. V.: The Effect of Sulfanilylguanidine on the Thyroid of the Rat. *Science*, 91:518, 1941.
10. Corwin, W. C., Jr.: Studies on the Chronic Toxicity of Sulfaguanidine. *Bull. Johns Hopkins Hosp.*, 69:39, 1941.
11. Firor, W. M. and Poth, E. J.: Intestinal Antisepsis with Special Reference to Sulfanilylguanidine. *Ann. Surg.*, 114:663, 1941.
12. Bornstein, S. and Strauss, L.: Selective Action of Sulfanilylguanidine on Different Salmonella Types and Its Practical Importance. *Proc. Soc. Exper. Biol. and Med.*, 47:112, 1941.
13. Rodaniche, E. C.: Sulfanilylguanidine and Sulfanilamide in the Treatment of Lymphogranuloma Venereum Infections of Mice. *J. Infect. Dis.*, 69:138, Sept.-Oct., 1941.
14. Richardson, A. P.: Comparative Effects of Sulfonamide Compounds as to Anemia and Cyanosis. *J. Pharm. and Exper. Therap.*, 72:99, 1941.

## Experiments on the Relationship of the Neurohypophysis to Gastric Secretion

By

E. G. GROSS, M.D., W. R. INGRAM, Ph.D.

and

N. W. FUGO, Ph.D.

IOWA CITY, IOWA

ON the hypothetical basis assuming that the posterior pituitary gland plays an important role in the control of gastric secretion and acidity, Metz and Lackey (1) have proposed the use of posterior pituitary extract in the treatment of peptic ulcer. Their interest in the relationship of peptic ulcer to a glandular disturbance was aroused by the frequency of nocturia in patients with this condition (2.)

It is well known that polyuria may be associated with dysfunction of the neurohypophysis. These authors (1) report an increase in both volume and acidity of the gastric secretion after removal of the posterior pituitary in dogs. Possible involvement of the anterior lobe or hypothalamus in these operations was not excluded, nor was evidence presented for completeness of the posterior lobe removal. The observations of Metz and Lackey (1) find some confirmation in the work of Blotner (3), who found that in patients with diabetes insipidus the secretory volume and gastric acidity were increased. Furthermore, De Ancias (4) has reported that injections of posterior pituitary extract produced a decrease in volume and acidity in normal men. Cutting, Dodds et al (5) have shown that in animals administration of posterior pituitary extract markedly decreases the gastric secretion, without modifying the acidity. After hypophysectomy, however, both volume and acidity were decreased (6.) All of these experiments were carried out by the use of stomach tubes, or by fistula into the whole stomach. Alterations in emptying time of the intact stomach may occur under the experimental conditions mentioned and lead to significantly different results. It is also probable that the dosages of posterior lobe extract in these various experiments produced concentrations of the hormone within the body exceeding any physiological level.

A possible connection between neurohypophysial function and gastric secretion was deemed of sufficient importance for further experiments on dogs with Pavlov pouches before and after pituitary stalk section. Severance of the pituitary stalk at a high level produces atrophy and practically complete loss of function of the posterior lobe with ordinarily minimal disturbance of the anterior lobe. Under such conditions the onset of a marked polyuria offers evidence of the success of the operation which cannot otherwise be obtained without histological examination. We feel, furthermore, that the use of Pavlov

pouch animals will tend to obviate any possible difference that may occur in emptying time of the stomach under the various experimental procedures.

### PROCEDURE

Healthy female dogs were selected and Pavlov pouches were constructed in two stages. The first consisted in making a stomach fistula with a piece of resected intestine according to the technique of Mann-Bollman (7.) After complete healing occurred, the second operation consisted in making a pouch of about 1/3 of the stomach according to the Pavlov technique. A fairly wide isthmus was left in order to obtain as much nervous innervation of the pouch as possible with this type of operation. Before closing the pouch a Pezzar catheter with a one-inch head was inserted through the fistula and retained by two silk sutures. Frequent oral administrations of milk were made throughout the experiment to test the intactness of the pouch. All animals which developed an opening between the pouch and stomach were discarded. We were able to carry seven dogs through the complete experiment without breakdown of the pouch occurring.

The animals were kept in metabolism cages and fed on our regular kennel diet. All animals maintained themselves in good nutritive condition throughout the experiment.

After complete healing of the pouch the animals were trained to stand quietly in slings and the gastric juice collected for six thirty-minute periods beginning 24 hours after the last meal. The first thirty-minute period collection was made without a stimulus. At the end of the first period a stimulus of either intramuscular injection of 1 mgm. of histamine or a meal of 150 gms. of Pard dog food mixed with 100 cc. of water was used. Some of the animals received only one of the stimulants throughout the complete experiment while in other cases both stimuli were used at different times in the same animal. Such experiments were performed with each dog once or twice a week. Conditioning of the animal did not seem to be a factor as there were no significant alterations in the first thirty-minute period as the animal became more accustomed to standing in the sling. The gastric samples were titrated for total acidity and free acidity by use of phenolphthalein and Töpfer's reagent. The pH was determined by use of a glass electrode Cameron pH meter.

After establishing a normal secretory response for the individual animal to either food or histamine or both, the animal's pituitary stalk was sectioned. The

operation was performed by a sub-temporal approach as developed by one of us (W. R. I.)

All of the animals made an uneventful recovery. The urine volume and water intake were measured for each dog for the balance of the experiment. All the animals developed a high degree of polyuria, averaging from 2000 cc. a day for the smaller dogs to 3500 cc. for the larger animals. The animals ate the regular kennel diet and maintained themselves in good condition without loss of weight. It has been

averaged. Composite curves expressing the means of these averages were plotted as shown in Fig. 1.

It will be noted that the only constant deviation of the post-stalk-section period occurs in the volume. The total volumes both after food and after histamine definitely tend to be decreased markedly after the first two thirty-minute collection periods. This result was consistently obtained in all animals except one. This dog gave slightly higher volumes after stalk section than during the control period, but the acidity re-

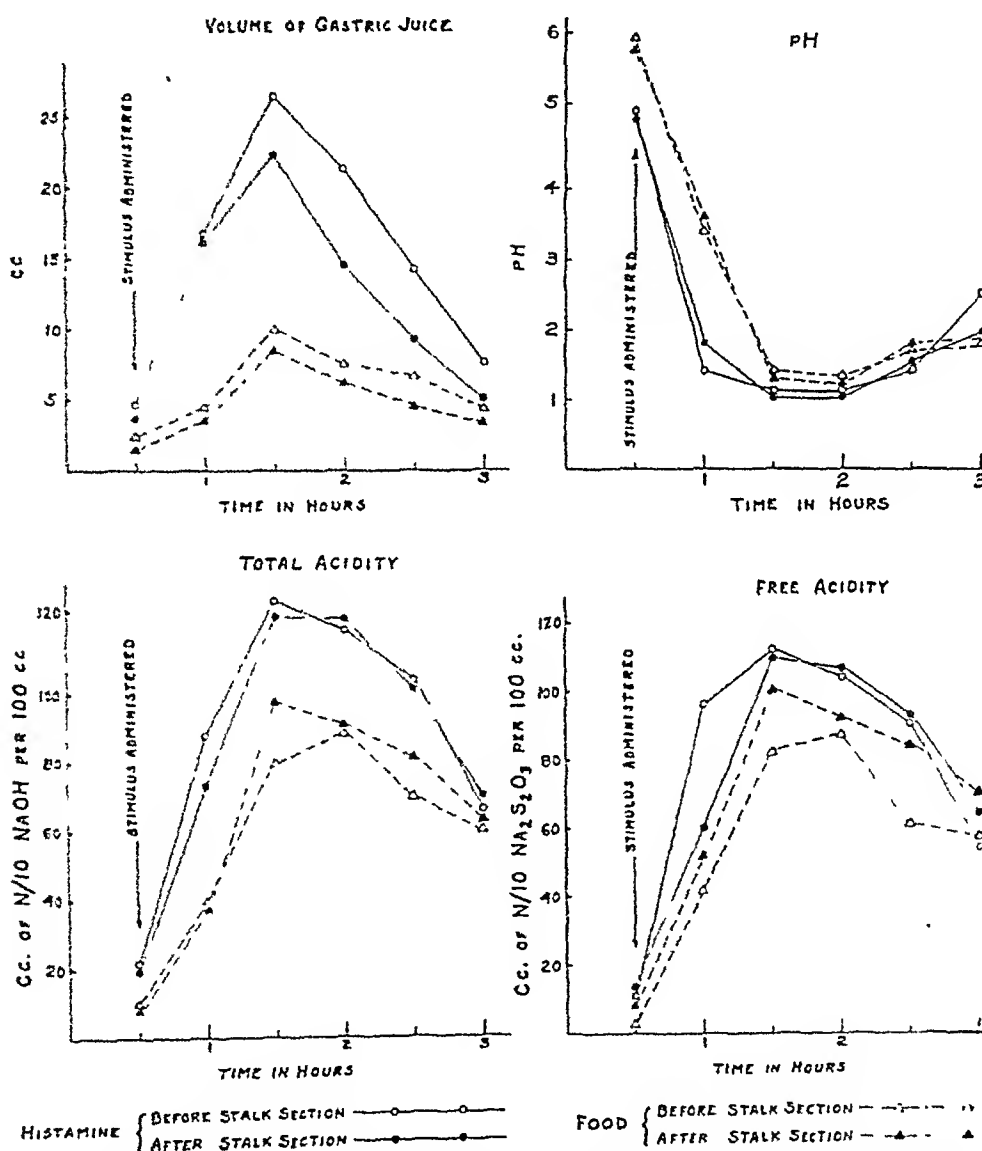


Fig. 1. Composite graphs showing the results obtained after histamine stimulation (average of six dogs) and after food stimulation (average of four dogs.)

shown by Ingram and Fisher (8), Magoun, Fisher and Ranson (9) and others that a high degree of permanent diabetes insipidus will only occur in the practically complete absence of posterior pituitary function. The collections of gastric juice were repeated as in the control period using the usual stimulus and also after the injection of Pitressin tannate in oil as a replacement therapy.

## RESULTS

The results obtained from each animal before and after stalk section both on food and histamine were

mained unchanged. It will be noted that the curves for pH values follow each other very closely, as is also the case with the total acidity. There is some divergence in the free acidity curve, but this is not a consistent result. From the average curve there is a slight increase in free acidity with food and slight decrease in free acidity with histamine. From the consistency in the pH and total acidity readings before and after stalk section the variation in free acidity is not considered of any significance.

In an attempt to restore an approximately normal condition in these animals, replacement therapy was

instituted. Table I indicates the effect of histamine on the secretory volume before and after Pitressin injection in one typical case. There were no significant alterations in the acidity values and therefore they are not cited.

Pitressin tannate in oil was used, as the slow absorption of this material probably simulates more closely the natural secretion of the gland than does

TABLE I

*Dog V volume of gastric secretion during 30 minute periods*

(in cc.)

| Collection periods                                    | 1   | 2    | 3    | 4    | 5   | 6   |
|---|-----|------|------|------|-----|-----|
| Control period (average of 5 runs)                    | 5.0 | 14.5 | 21.0 | 14.8 | 7.0 | 3.7 |
| After stalk section (average of 5 runs)               | 2.0 | 12.0 | 16.0 | 7.5  | 3.0 | 2.5 |
| After Pitressin and stalk section (average of 2 runs) | 5.2 | 13.0 | 17.5 | 12.0 | 9.0 | 6.0 |

the injection of a solution of posterior pituitary. In all instances the injection of 1 cc. of Pitressin tannate reduced the polyuria very markedly for several days. Gastric secretion collections were made in most instances 24 hours after the injection of the Pitressin while a few were collected at the end of 48 hours which corresponded to the height of its effect on the polyuria. In all instances the only significant change that occurred was a tendency for the volume to increase towards the level of the normal control period, i.e. the pre-stalk-section period. It is perhaps significant to note that two dogs were given Pitressin tannate before stalk section and there were no alterations in either gastric volume or acidity.

In order to determine whether the decrease in volume after stalk section was directly due to the absence of neurohypophysial function or due to the dehydration that apparently occurs in diabetes in-

TABLE II

*Dog V volume of gastric secretion during 30 minute periods*

(in cc.)

| Collection periods                           | 1   | 2    | 3    | 4    | 5   | 6   |
|--|-----|------|------|------|-----|-----|
| Before stalk section (average of 5 runs)     | 5.0 | 14.5 | 21.0 | 14.8 | 7.0 | 3.7 |
| After stalk section (average of 5 runs)      | 2.0 | 12.0 | 16.0 | 7.5  | 3.0 | 2.5 |
| After subcutaneous water (average of 2 runs) | 5.2 | 16.0 | 18.0 | 12.0 | 6.0 | 4.3 |

sipidus when the animal is deprived of water for a three hour period, we decided to administer subcutaneous water during collections. Three animals were used for this experiment and 100 cc. of sterile tap water were injected into the loose neck tissues in divided doses. This amount of water corresponded to the average urine excretion of two of the dogs when deprived of water for a three hour period.

Table II represents the volume secretion of the same dog as shown in Table I when given subcutaneous water.

While the volume is slightly below the normal secretion, there is a decided increase over that during the stalk section period when no water was given. The pH, total acidity and free acidity were not altered by this increase in volume.

## DISCUSSION

Our results with dogs do not substantiate the findings of Metz and Lackey (1) that both volume and acidity of the gastric juice increases after removal of the posterior pituitary. These workers do not state whether their animals developed diabetes insipidus. With complete removal or dysfunction of the posterior lobe dogs will develop this condition. Our dogs all developed a permanent polyuria, demonstrating the loss of functional neurohypophysial tissue. There was a minimum of anterior pituitary disturbance in our animals also.

Blotner (3) also found in the human patient with diabetes insipidus an increase in gastric volume and gastric acidity. It is difficult to explain the difference between his clinical findings and our experimental results. Perhaps the divergence indicates that there is a species difference or that in human diabetes insipidus there is an alteration in the emptying time of the stomach which might affect the results. Metz and Lackey (1) report that in their dogs with posterior lobe removal there is a heightened motility and spasticity of the stomach as compared to normal animals. We have no check on this finding. Perhaps psychic conditions in Blotner's patients contributed to alteration in gastric secretion. It is known that conditions of tension influence gastric acidity and it is conceivable that there may be certain elements of strain and worry connected with a severe polyuria.

Cutting, Dodds et al (6) found in their completely hypophysectomized cats a decrease in gastric volume and acidity. It is well known, however, that complete hypophysectomy markedly disturbs the general metabolism. In our experimental animals the only major disturbance is in the water balance. We could observe no significant effect of posterior pituitary extract administration other than that which might be interpreted as due to a restoration of normal water balance. After injection of Pitressin tannate in two dogs before stalk section, there were no changes in gastric volume or acidity. However, our method of administration differs from that of Cutting, Dodds et al (5.) It is quite possible that immediately after injection of large doses of posterior pituitary solution there might be major alterations in the blood supply to the stomach and thus more or less decrease in gastric secretion. With the slow absorption of Pitressin tannate there should be a minimum of vascular disturbance.

Four of the dogs were autopsied, and careful examination of the stomach mucosa showed no evidence of any ulceration having occurred.

## CONCLUSIONS

(1) Studies on gastric secretory response to histamine and food on Pavlov pouch dogs with practically complete dysfunction of the posterior pituitary showed no alteration in the acidity of the gastric juice. There

was a decrease in volume which was probably caused by the mild dehydration occurring in these polyuric animals during the three hour test period.

(2) The injection of Pitressin tannate into normal

pouch dogs produces no alteration in either volume or acidity; after pituitary stalk section the injection of this drug tends to raise the volume towards the normal secretory level without altering the acidity.

#### REFERENCES

1. Metz, M. H. and Laekey, R. H.: Peptic Ulcers Treated by Posterior Pituitary Preparations. *Am. J. Dig. Dis.*, 7:27, 1940.
2. Metz, M. H. and Laekey, R. H.: Peptic Ulcers Treated by Posterior Pituitary Preparations. *Texas State J. Med.*, 32:589, 1937 and 34:214, 1938.
3. Blotner, H.: Gastric Analysis and Gastric Symptoms in Diabetes Insipidus. *Am. J. Dig. Dis.*, 7:73, 1940.
4. De Ancinas, C. J. H.: Insuline, Pituitrine et Secretion Gastrique. *Compt. Rend. Soc. de Biol.*, 95:313, 1926.
5. Cutting, W. C., Dodds, E. C., Noble, R. L. and Williams, P. C.: The Effect of Posterior Pituitary Extract on the Alimentary Secretions of Intact Animals. *Proc. Royal Society, London*, 123: 27, 1937.
6. Cutting, W. C., Dodds, E. C., Noble, R. L. and Williams, P. C.: Gastric Secretion and Blood Flow in Hypophysectomized Animals. *Ibid.*, 123:49, 1937.
7. Mann, F. C. and Bollman, J. L.: A Method for Making a Satisfactory Fistula at Any Level of the Gastro-Intestinal Tract. *Ann. Surg.*, 93:794, 1931.
8. Ingram, W. R. and Fisher, C.: The Relation of the Posterior Pituitary to Water Exchange in the Cat. *Anat. Rec.*, 66:271, 1936.
9. Magoun, H. W., Fisher, C. and Ranson, S. W.: The Neurohypophysis and Water Exchange in the Monkey. *Endocrinology*, 25:161, 1939.

## Stricture of the Rectum Due to Lymphogranuloma Venereum---Symptoms and Treatment With Sodium Sulfanilyl Sulfanilate

By

JOSEPH G. LEVY, M.D.,\* ERNEST C. HOLDER, M.D.†

and

JESSE G. M. BULLOWA, M.D.‡

NEW YORK, NEW YORK

THE etiologic agent of Lymphogranuloma Venereum was shown by Hellaström (1) to be a filterable virus. In 1928 Frei and Koppel (2) reported positive Frei tests in five patients with rectal stricture. Since then Cole and others (3, 4) have confirmed the now generally accepted observation that Lymphogranuloma Venereum is responsible for rectal strictures. When inflammatory rectal strictures occur, a Frei test (5) may support the diagnosis of virus etiology even though genital lesions are absent.

#### OLD METHODS OF TREATMENT

Prior to April, 1940, treatment for rectal stricture due to Lymphogranuloma Venereum, as carried out at the Proctologic Clinic of Harlem Hospital Out-Patient Department, was either surgical, biological or chemical.

##### Surgical

Surgical treatment was employed in those rectal strictures which presented increasing obstipation or intestinal obstruction, or where the strictures did not admit the tip of the examining finger. Whether dilatation or colostomy was performed was determined by the degree and site of intestinal involvement. Colostomy was usually performed for strictures at or above the recto-sigmoid junction. The colostomy was permanent and was done not only to relieve acute obstruction, but to divert the fecal stream from the ulcerated colon. In a few cases resection of the rectum was performed and the sphincter was preserved. Except in two or three cases, the results obtained from mobilization of the rectum and excision of the rectal stricture were not satisfactory. In many of these

patients the lumen of the rectum continued to contract and a new stricture formed.

##### Biological

Repeated injections of Frei Antigen (6) were used in more than 30 patients. The treatment was discontinued because it was found that the severity of the symptoms was only temporarily lessened and usually recurred after treatment was discontinued.

##### Chemical

With its advent, sulfanilamide (7) was employed in the treatment of many patients, but was found too toxic for prolonged use. The majority of sufferers from this disease have a secondary anemia (8) which is made worse by sulfanilamide. Reduction of the discharge was the only improvement in patients treated with sulfanilamide. This effect might have been brought about by the action of the drug upon a secondary invader rather than on the virus (9.) Other sulfonamide derivatives have been employed (10, 11.) Hebb, Sullivan and Felton reported that sodium sulfanilyl sulfanilate was effective against the virus (12.) Since April, 1940, we have devoted our attention to determining the effect of sodium sulfanilyl sulfanilate\* on Lymphogranuloma Venereum stricture. Elsewhere we have shown that sodium sulfanilyl sulfanilate in vitro has an inhibitory effect on the virus of Lymphogranuloma Venereum (13.)

##### Clinical Observations

All of the patients under treatment were in the chronic tertiary stage with well advanced rectal stricture. As has been observed (6) by others, we found the disease is most frequent in women. Most of the patients were in the 30-39 year group.

Of 102 patients in whom the symptoms were both gastro-intestinal and constitutional, constipation oc-

\*Associate Surgeon in Proctology, Surgeon in Charge of Rectal Clinic, Harlem Hospital, New York, N. Y.

†Assistant in Pathology, Harlem Hospital.

‡Clinical Professor of Medicine, New York University, College of Medicine, Visiting Physician, Harlem Hospital, Visiting Physician, Willard Parker Hospital.

From the Medical and Surgical Services of Harlem Hospital, Department of Hospitals, New York, N. Y.

Submitted January 30, 1942.

\*Received through the courtesy of Dr. W. G. Malcolm, Lederle Laboratories, Inc., Pearl River, New York, N. Y.



curred in 56% or 57 patients. It was never severe. It is attributable in part to diminished motility of the diseased sigmoid. In some cases only liquid stools are passed and the fecal column is stagnant.

Acute or primary proctitis may be produced by direct implantation of the virus on the mucosa of the rectum (14), or it may be due to lymphatic spread of the virus from vagina or cervix. Few of our patients gave a history of pederasty or sodomy. Among these patients proctitis was present with the stricture and occurred in 66% or 67 patients.

After infection with pyococci, the rectum may become denuded and ulcerated accounting for the bloody purulent discharge which occurred in 47% or 48 of 102 patients. Because they are in part produced by the impaction of fecal material, ulcerated areas are usually located cephalad to the stricture area.

Bleeding is a frequent symptom and in uncomplicated cases may be attributed to erosion of blood vessels in the ulcerated area. This symptom occurred in 61% or 62 of the 102 patients.

Tenesmus usually occurs with rectal stricture and if present is mild. Tenesmus was present in 15% or 15 of the 102 patients.

Pain, which may be due to pressure, to the proctitis, or to ulceration was encountered in 45% or 46 of 102 cases.

These patients have a low haemoglobin and a low red blood cell count, and the white blood cell count is increased (15.) Secondary anemia with loss of weight was frequently encountered. Anemia and the absorbed toxic products account for the asthenia.

Arthralgia appeared in 5% or 5 of 102 patients and was either transitory or persistent. In some of our patients it was the only symptom. A positive Frei test when joint pains are present may be enough to suggest that Lymphogranuloma Venereum is responsible for them. One such patient later developed a rectal stricture.

#### *Rectal Strictures*

Rectal strictures may be of the diaphragmatic, the tubular or the hour-glass variety. Among our patients the diaphragmatic type of stricture was usually found in men. They occurred one and one-half to two inches from the anal orifice. Tubular strictures are more common in females (16.) The stricture may be low, medium or high. Strictures may skip the rectum entirely and occur in the colon (17.)

In the acute process the mucosa of the rectum is granular and there are many ulcerated or eroded areas. In the more chronic process, the mucosa becomes adherent to the underlying muscularis and there are many firm fibrous and ridge-like linear elevations and also a marked perirectal infiltration.

In old cases with rectal stricture caused by Lymphogranuloma Venereum virus complications may occur singly or there may be several in the same patient. The most frequent complications are due to the edema of the diseased mucosa and perirectal tissues or to direct involvement of adjacent organs.

#### THE NEW TREATMENT

When the diagnosis was established the patients were given 5.0 grams of sodium sulfanilate as an initial dose, and 0.5 grams three times a day thereafter without interruption. In many instances the

patients were given a week's supply of the drug on their visit to the Out-patient Department so that they were compelled to return for examinations. Sodium sulfanilyl sulfanilate was not toxic. When administered in either small or massive doses, untoward systemic or local disturbances attributable to it were rare. One patient who had received 5.0 grams four times a day developed a severe diarrhea, which subsided when the dose was reduced. Hospitalized patients were given the drug intravenously in doses from 1.0 to 5.0 grams twice daily. By this route an increased concentration in the blood may be maintained but there was no benefit which could not have been obtained by oral administration, and it is not practical nor necessary to prolong the stay of these patients in the hospital.

In all, one hundred and eighteen patients suffering from stricture due to Lymphogranuloma Venereum were treated with sodium sulfanilyl sulfanilate. Many of them had received several forms of chemotherapy over periods lasting from two years to twenty years.

After a relatively short period, 3 to 4 weeks, there was more striking improvement with sodium sulfanilyl sulfanilate than with any treatment previously employed. The anemia diminished as evidenced by the increase in the red blood cell count and hemoglobin, there was gain in weight, and diminished edema and regeneration of the rectal mucosa, with relief of symptoms.

Since using sodium sulfanilyl sulfanilate we found it necessary to use dilatation in only 4 patients, 5% of our cases as against 75% in 150 patients previously. None of the patients under treatment with sodium sulfanilyl sulfanilate required colostomy. In spite of prolonged treatment the patients continued to have a positive Frei test. Improvement in the clinical condition of all the patients warranted further administration.

In many patients there was complete disappearance of symptoms. There was marked reduction and (in some patients complete disappearance) of rectal bleeding after treatment for six months. Usually symptoms became ameliorated only after three or four weeks of drug administration. The edema diminished and though the fibrous tissue is not affected, the stricture became less narrow. When the edema and infiltration subside, instead of admitting only the tip, the entire finger may penetrate the stricture and well-formed stools are passed.

In a few cases where the discharge persisted, sulfathiazole was employed either alone or with sodium sulfanilyl sulfanilate. The discharge disappeared in most of these cases. It is thought that persistent discharge was due to secondary bacterial infection which required sulfathiazole. It would have been undesirable to give the sulfathiazole for extended periods because it is absorbed and excreted through the kidneys. The beneficial local effect may be obtained with the less toxic drug. These patients may require treatment for several years.

#### SUMMARY AND CONCLUSIONS

Proctitis and rectal stricture due to Lymphogranuloma Venereum have been greatly benefited by poorly absorbed and non-toxic sodium sulfanilyl sulfanilate. The local symptoms disappear, the mucosa regenerates, and edema and infiltration recede so that the

stricture is wider, permitting normal evacuation of the bowel. No surgical treatment other than dilatation has been necessary in patients treated with sodium sulfanilyl sulfanilate.

Administration of the drug resulted in gain in weight and an increase of red blood cells. Improvement appears only after three to four weeks of drug ad-

ministration and it must be continued for a long time (several years.) In a few patients a discharge which was apparently due to a pyogenic organism resistant to sodium sulfanilyl sulfanilate yielded to sulfathiazole. In these patients treatment with sodium sulfanilyl sulfanilate was resumed and successfully continued.

## REFERENCES

1. Hellerstrom, S. and Wassen, E.: Etude du virus de la Lymphogranulomatose Inguinale. *Comp. Rend. Soc. de Biol.*, 106:502, 1931.
2. Frei, W. and Koppel, A.: Ulcus vulvae chronicum elephantiasium (Esthionieme) und sogenanntes Syphilome anorectal als Folgeerscheinungen der Lymphogranulomatosis inguinalis. *Klin. Wchnschr.*, 7:2331-2336, Dec. 2, 1928.
3. Cole, H. N.: Lymphogranuloma Inguinale, the Fourth Venereal Disease; Its Relation to Stricture of the Rectum. *J. Am. Med. Ass'n.*, 101:1069, 1933.
4. Bensaude, R. and Lambling, A.: Maladie de Nicolas-Favre et lésions norectales: sténose ano-rectites simples, fistules isolées. *Paris M'd.*, 1:361, April 30, 1932.
5. Frei, W.: Eine neue hautreaktion beim Lymphogranuloma Inguinale. *Klin. Wchnschr.*, 2148, 1925.
6. Wien, M. S. and Perlstein, M. O.: Intradermal Treatment of Lymphogranuloma Inguinale. *Brit. J. Dermat.*, 49:63, 1937.
7. Shropshire, G.: Sulfanilamide in Treatment of Strictures of the Rectum Caused by Lymphogranuloma Venereum. *Illinois Med. J.*, 74:153, 1938.
8. Wilmoth, C. L.: Subneute Inguinal Lymphogranulomatosis. *Southern Med. J.*, 21:108, 1928.
9. See 7.
10. Gurie, N. J.: Neue wege in der Behandlung des Lymphogranuloma Inguinale. *Munch. Med. Wchnschr.*, 85:335, 1938.
11. Earle, K. V.: Lymphopathia Venereum Treated with M. & B. 693. *Lancet*, 1:985, 1939.
12. Hebb, A., Sullivan, S. G. and Felton, L. D.: Treatment of Lymphopathia Venereum with Sodium Sulfanilyl Sulfanilate and Sodium Sulfanilate. *Pub. Health Rep.*, 54:1750, 1939.
13. Holder, E. C., Levine, S. and Bullock, J. G. M.: In Vitro Action of Sulfonamides on Lymphogranuloma Venereum Virus. *J. Pharm. and Exp. Ther.*, 74:99, 1942.
14. Grace, A. W. and Henry, G. W.: The Mode of Acquisition of Lymphogranuloma Venereum of Anorectal Type. *N. Y. State J. Med.*, 40:285, 1940.
15. De Wolf, H. F. and Vnn Cleve, J. V.: Lymphogranuloma Inguinale. *J. Am. Med. Ass'n.*, 99:1065, 1932.
16. Torpin, Richard, Lund, E. R., Greenblatt, R. B. and Sanderson, E. S.: Lymphogranuloma Venereum in the Female. *Am. J. Surg.*, Vol. XLIII, No. 3, 688:694, 1939.
17. Coutts, W. E., Opazo, L. and Montenegro, M.: Digestive Tract Infection by the Virus of Lymphogranuloma Inguinale. *Am. J. Dig. Dis.*, 7:287, 1940.

## Editorial

### A REMARKABLE STUDY OF 10,890 CASES OF CANCER OF THE STOMACH\*

AN event of outstanding importance to gastro-enterology was the recent publication by Drs. Walters, Gray, Priestley and several collaborators of a remarkable statistical study of 10,890 cases of carcinoma of the stomach seen at the Mayo Clinic in the years from 1907 to 1938 inclusive. After Dr. E. B. Lewis had spent a year going over the records and taking off the essential data, the information was transferred to punch cards and the statistical analysis was made under the supervision of Dr. Joseph Berkson. As Dr. Berkson said, even when one has nearly 11,000 cases of a certain disease, the number is not large enough when one starts to break the material down into groups, for comparison, let us say, of the end results of different types of operations. The trouble is that to get trustworthy results one must break these groups down still further, according to the age and sex of the patient, the degree of malignancy of the lesion, the presence of metastasis, and other highly important factors. Then the first thing one knows one has little groups too small for the drawing of trustworthy conclusions.

One great advantage of this study is that the 10,890 patients were studied in one institution by one group of men. Another most noteworthy feature is that the follow-up of the cases was so nearly complete. Usually in statistical studies about a third of the patients do not answer the questionnaire and cannot be traced, and then the results of the analysis are badly vitiated by the impossibility of knowing whether the patients who didn't answer were dead, or whether they were so well that they didn't care to be bothered any more about their old trouble. In order to remove this most disturbing defect in the analysis, a tremendous effort was made to get information as to what happened to

every patient seen, and actually, more than 99 per cent were kept track of for at least five years!

Another highly important step taken during this study was the development of new methods for plotting the number of survivals. Fig. 1 shows how easy it is now to see the difference between the survival rates year by year of an apparently normal group of persons (with an average age around fifty-five years, the same as that of the cancer-bearing group) and the corresponding rates of patients with carcinoma of the stomach. Most surgeons who in the past have reported survival rates after resections of the stomach for cancer have done themselves a little injustice in failing to "adjust" their data for the normal death rate of persons past middle age. They forgot that if they had taken, let us say, the appendix out of 100 persons with an age averaging around fifty-five years, they would have had only ninety-two left at the end of five years. Obviously, then, the survival rates observed in any group of persons operated on well past middle age should be adjusted. If this is not done, the figures as obtained will be a little more discouraging than they need to be.

Another interesting point brought out by this study is that there is a justification for the current practice of assuming that when a patient has lived for five years after the removal of a cancer, he can be looked on as cured. Proof of this is to be found in Fig. 1, where it will be noted that for the first five years after the removal of a carcinoma of the stomach, the curve representing the survival rate falls more steeply than does the curve of survival for normal persons of fifty-five years of age, but after the five year mark, the lines are fairly parallel, suggesting that most of the patients operated on now have no more cancer cells left in their body, and that when some die, they die of the usual diseases that affect older persons.

A fact which emerges strikingly from this study is the great prognostic significance of the degree of ma-

\*Walters, Waltman, Gray, H. K. and Priestley, J. T.: Carcinoma and Other Malignant Lesions of the Stomach. Philadelphia, W. B. Saunders Company, 1942, 576 pp.

lignancy of the lesion as expressed on Broders' scale. Thus, in Fig. 2 it will be seen that at the end of five years, 60 per cent of the persons from whom a carcinoma graded 1 or 2 had been removed, and who recovered from the operation, were alive; 29 per cent of those whose tumor was graded 3 were alive, and only 21 per cent of those whose tumor was graded 4 were alive.

A curious finding which doubtless explains what happens in some of those cases in which a patient with

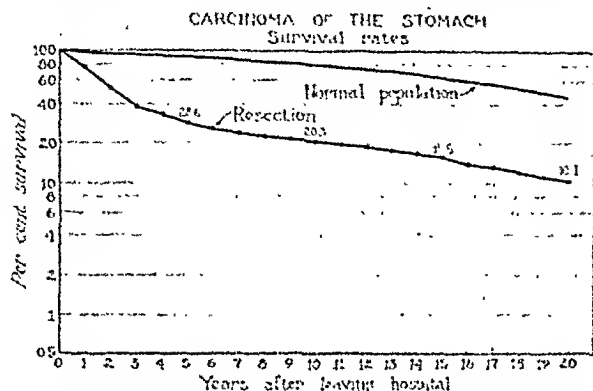


Fig. 1. Survival rates following resection of the stomach compared with the mortality rates among normal persons in comparable age groups. [From Walters, Waltman, Gray, H. K. and Priestley, J. T.: *Carcinoma and other malignant lesions of the stomach*. Philadelphia, 1942, 576 pp., courtesy of W. B. Saunders Company, publishers.]

proved cancer of the stomach appears to recover after treatment by Christian Science or by some quack's serum is that after five years, 1.2 per cent of the patients who had only a palliative operation done were alive, and 0.7 per cent who were simply explored were alive. Every physician of experience knows that at times the cells of the body and those of the carcinoma seem to fight each other to a stalemate, which then lasts for years. When patients have to be told that they have an inoperable carcinoma, they should always be reminded of this fact.

years. When patients have to be told that they have an inoperable carcinoma, they should always be reminded of this fact.

The outstanding finding, of course, is that cancer of the stomach is not so hopeless a disease as most physicians believe today. One of the reasons why patients are now being operated on so late is that so many physicians and patients feel that a man with a cancer of the stomach is just doomed. Actually, if he would only get to a surgeon while the lesion was still resectable, he would not necessarily be doomed. The sad fact is that today 51 per cent of the patients who begin to have symptoms are treated medically for more than a year before they get into the hands of a surgeon. Largely as a result of this delay, only 57 per cent of the patients with this disease who go to the Mayo Clinic are worth exploring, and only 25 per cent have a lesion that can be removed.

In this study, 24 per cent of those who had the lesion removed and who recovered from the operation were alive five years later. Of those who had no visible metastasis, 36 per cent were alive five years later, and of those with a tumor graded 1 or 2, 60 per cent were alive five years later. Doubtless these figures

could be greatly improved if only patients with gastric cancer would go to a good physician a few days after symptoms appear, and if then the physician would be keenly alive to the danger of treating medically anyone, especially past middle age, who has a short history of indigestion and any type of deformity in the stomach.

Some persons still put off operation today because they fear the immediate mortality of resection. There is no question that even in the hands of the ablest surgeons available, this mortality is considerable, but the patients should remember that without operation the mortality is almost 100 per cent. Actually, in this series of cases the hospital mortality following resection for gastric carcinoma ranged from around 5 per cent for patients in the thirties to around 25 per cent for patients in the seventies.

It is interesting to note that in 52 per cent of the cases the first symptom experienced was indigestion, and in 28 per cent the symptoms were those of ulcer. Tremendously significant is the fact that in 80 per cent of the patients with hunger pain, good relief was obtained for a while with a Sippy type of management. Eleven per cent of all the patients complained only of a vague abdominal distress; 8 per cent just went into a decline, and 1 per cent noted hematemesis. Eighty-six per cent noticed loss of weight; 81 per cent had some vomiting or regurgitation or other signs of obstruction at the pylorus; 42 per cent had epigastric pain of an obstructive type; 36 per cent had pain which might be interpreted as due to ulcer; 35 per

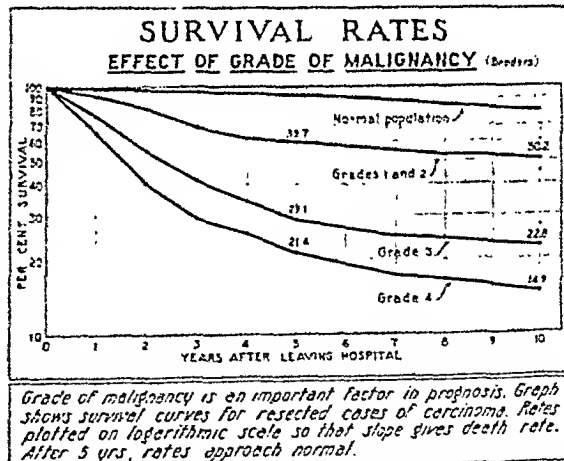


Fig. 2. Survival curves for resected cases of carcinoma. [From Walters, Waltman, Gray, H. K. and Priestley, J. T.: *Carcinoma and other malignant lesions of the stomach*. Philadelphia, 1942, 576 pp., courtesy of W. B. Saunders Company, publishers.]

cent noticed anemia; 33 per cent felt tired and uncomfortable; 30 per cent became constipated, and this is an important point. This symptom was due partly to the reduction in the amount of food eaten and partly to pyloric obstruction. Interestingly, 27 per cent of the patients lost their appetite. Seven per cent complained of pain in the back.

A curious fact which seems rather paradoxical is that in the case of 1127 patients who had had symptoms for less than three months, resection of the

## The War's Challenge to Gastro-Enterology

### Presidential Address

By

RUSSELL S. BOLES, M.D.  
PHILADELPHIA, PENNSYLVANIA

THE American Gastro-Enterological Association was founded on June 3, 1897, in the office of Dr. D. D. Stewart in Philadelphia by a small group of eight physicians who, as they said of themselves "were especially interested in diseases of the stomach, intestines and their appendages." In their original constitution these gentlemen stated "The object of this Association shall be the promotion of all that appertains to diseases of the digestive tract." Three of this group are living today. One of them, Dr. Max Einhorn, served as president of the Association at its third annual meeting in 1899, and this evening will be awarded the Friedenwald Medal as a humble recognition on the part of this Association of the esteem in which he is held. Dr. Charles D. Aaron of Detroit, Michigan, and Dr. Allen A. Jones of Buffalo, New York, are the other two founder members whom we are so proud of having today as Honorary Members of the Association. Both of these gentlemen served as officers of the Association with fidelity and distinction. Dr. Jones was president in 1921 and Dr. Aaron was secretary-treasurer for fourteen years, having been elected in 1897.

After forty-five years it is befitting that your Association should consider how well and to what extent it has contributed to the promotion of gastro-enterology. More particularly should you appreciate the fact that your stature will be measured by the manner in which you meet those opportunities that normally lie ahead and especially those that will be created by the present emergency. The opportunities will be great; to make the best of them will not be easy. Vision will be required and accomplishments other than those already to your credit will be expected of you. Without vision and initiative you cannot hope to equal the achievements of your founder fathers, who though only eight in number, boldly adventured into unknown fields and distinguished themselves in such manner that they were commended and honored by affiliation with some of the great foreign personalities of their day. May I read to you several letters from individuals, the mention of whose names will arrest your attention and arouse your greatest admiration:

Berlin, No. 4 Rauchstrasse, 24.6.1901

(Translation)

Much honored Colleague:

I am in receipt of your communication of the 7th of June in which you inform me of my unanimous election to the honorary membership in the American Gastro-Enterological Association and I beg you to express to the Association my deep-felt thanks for the honor it has shown me.

I wish at the same time to say that I am gratified to see that the representatives of the science of the

diseases of the digestive tract which are evidently becoming influential in your land have constituted themselves into an organization of their own. Your country is open to true progress in every direction and furthers it with genuine enthusiasm. I hope that your organization will enrich further the stock of our information and that a helpful reaction will come through you to the physicians of countries outside of America.

I am the more proud of the distinction you have conferred upon me by this election of yours and take more satisfaction out of it, since not a few of the members of your Association are personal friends and pupils of mine. I esteem this honor they have given me as a mark of their recognition of the modest service I have rendered to science and as a warrant of their further development of it.

I hope I may some day be able to express my warm thanks personally to the Society.

Until then I am with best regards and wishes for the prosperity of the American Gastro-Enterological Association.

Very devotedly,

Prof. Dr. Ewald  
Geheimer Medizinal Rath.

Heidelberg, 1 July, 1901

(Translation) <sup>3</sup>

Dr. Charles D. Aaron,  
Secretary the the Gastro-Enterological Society.  
Much honored Sir:

Pardon that I answer your letter of the 7th of June only today. I have been prevented through illness. I feel very grateful for the great honor your Society has accorded me and beg you to convey my thanks to the very valued members of the Gastro-Enterological Society.

Accept the assurance of my high regard for yourself, my dear colleague.

Your very devoted,  
Dr. Kussmaul.

Giessen, 27 June, 1901

(Original in English)

To the American Gastro-Enterological Association  
to hands of Mr. Charles D. Aaron, M.D.  
Secretary and Treasurer.

For the great honor, which the American Gastro-Enterological Association, presided over by such illustrious men, has conferred upon me, by electing me a corresponding member, I allow me to return my best thanks. I am appreciating very much that great distinction whenever being obliged to tell me, that I am scarcely worthy of it.

I request you, Sir, to return to the Association my best and devoted thanks, affirming at the same time,

that as in my power, I will endeavor also in future, to cooperate to the increase of our Science, including such illustrious men of science.

Very respectfully yours,  
Franz Riegel.

Berlin, 8 July, 1901  
N. W. Alexandrofer, 6

(Translation)

Dr. Charles D. Aaron, in Detroit,  
Much honored Colleague:

I thank you as well as the entire Board of your highly esteemed Society most heartily for the honor you have accorded by electing me as Corresponding Member of the Gastro-Enterological Society. I add also my best wishes for the prosperity of this Society of yours which I deem most timely and which I believe will undoubtedly be imitated in Europe in due time.

My acknowledgement is tardy for the reason that your letter was defective in the address and reached me on that account only three days ago.

Accept my dear Mr. Secretary the assurance of my sincere respect and I beg you to convey the same to the members of your Society.

Always your obedient,  
J. Boas.

Vichy, 27 June, 1901

(Translation)

Mr. Secretary and much honored Colleagues:

I am very proud of the title of Corresponding Member which the American Gastro-Enterological Association has been kind enough to transmit to me through your amicable intervention. I beg you to express for me to your eminent colleagues my grateful acceptance of the same and to tell them that I wish to evidence, through some later work of mine, to some degree at least, as far as I can, how much I value this proof of their esteem for me.

Please accept for yourself, Mr. Secretary, my best regards,

Glenard.

June 28, 1901  
29 Hatley St., Cavendish Square, W.

Dear Dr. Aaron:

I feel highly honored by the wish of your Society to elect me a corresponding member. The well deserved reputation of so many of its members is a guarantee that valuable work will be the result of their labor.

I am dear Dr. Aaron.

Yours very sincerely,  
Samuel Fenwick.

29.6.1901

(Translation)

Much honored Colleague:

I have heard with much pleasure of my election to honorary membership in the American Gastro-Enterological Association and wish to say in response that I shall deem it a great honor to be counted amongst the members of the Association. Please express to the Board of the highly honorable Society my heartfelt thanks for the honor they have accorded me and my

expression of my special regard in every spirit of collegueship.

Yours devotedly,  
Dr. William Leube,  
Professor of Medicine.

That your Association has had vision and has been active in the promotion of gastro-enterology is attested in several ways, to some of which I shall briefly refer.

The activities of an Association such as this, devoted to a specialty in medicine, unfold themselves in two ways—curricular and extracurricular as it were. The curricular activities are devoted to holding an annual scientific meeting at which original developments of a clinical and research nature are presented and discussed for our mutual advantage. Those articles and discussions that are deemed of merit are published in the official Journal of the Association. The establishment and elevation of this Journal to its present commendable position is due entirely to the efforts and ability of the group of individuals who so capably assumed the responsibilities entrusted to them in the formation and development of the Journal. I refer particularly to the members of the original Journal Committee who labored under great difficulties in finally bringing it to publication, and to Dr. Alvarez and his editorial staff in establishing and maintaining it on a high professional and scientific level. Aside from serving as a means of disseminating useful information on gastro-enterological subjects it has relieved the Association of the expense of the publication of its Transactions which now appear in a volume of the Journal reserved for this purpose.

The programs of the annual meetings are showing constant improvement—an improvement that can be gauged by the quality of the material presented and the widening diversification of subjects covered. Great impetus in stimulating more scientific work especially of a research nature within your Association was created by the admission to membership of some of the leading research workers in this country and Canada in the fields of physiology and biochemistry. The research members have so distinguished themselves in this Association, and indeed in the profession at large that, if the internists do not show more promise of keeping pace with their brilliant ambitious accomplishments, the tail will soon be wagging the dog instead of the dog the tail. To still further broaden the compass of its objectives it now remains for the Association to admit to its membership representative specialists from the fields of pathology, psychiatry and psychology. There is perhaps no field in internal medicine that is more closely related to, nor more directly dependent upon developments in psychosomatic medicine than gastro-enterology, inasmuch as a number of diseases of the digestive tract are influenced, if not primarily caused, by disorders of the brain and nervous system. Therefore inclusion of the experimental psychologist and psychiatrist within our ranks should prove of the utmost benefit.

It is a matter of interest to record at this point that it was not until the middle of the nineteenth century that experimental investigation began to assume some degree of prominence—prior to this time the progress of medicine was solely of a clinical nature. The work of Beaumont had stirred the imagination of those at



home and abroad and a fire of experimental research was kindled that burns brightly and afar today. It is unfortunate, however, that too often our colleague in research is indifferent to or unfamiliar with essential clinical facts and his deductions are accepted with finality instead of serving as guidance for further clinical study. On the other hand the clinician is rarely an experimental investigator of parts and frequently is unaware of the activities of the physiologist and biochemist with the net result that both experimental and clinical medicine are retarded in their development. Such a situation leads to a certain degree of isolationism in our profession, and this carries with it the same handicaps and disadvantages of any other form of isolationism. It was with creditable foresight therefore that your Association, several years ago, broadened its membership and thereby provided opportunity for men of different minds to gather on common ground for the purpose of discussing controversial problems of which, unfortunately, there is an abundance in gastro-enterology.

I would like now to take you back in the history of our specialty to its very beginning, to the dawn of the nineteenth century. It was at this time that the stomach tube was first used, presumably by John Hunter. Its possibilities were not generally recognized, however, until eighty years later when Kussmaul described its use in the treatment of dilatation of the stomach. With the advent of the stomach tube came the development of the test meal by Leube and Riedel and the discovery of free hydrochloric and other acids in the stomach by Ewald and Boas. During this time enthusiastic and promiscuous use of the tube was being made in the treatment of various affections of the stomach. As a result of all this, increasing interest was being developed in clinical gastro-enterology and eventually the vision of a gastro-enterological association came to the little group of men who met in the office of Dr. Stewart just forty-five years ago. For familiar sounding reasons, some of which may have been justified, this group of "stomach specialists" was met with hostility by the imperious internists of the day. It was probably true in that day, just as it is today, that many of those who called themselves "stomach specialists" reflected little or no credit on the profession, not only because of an absolute lack of training for the specialty itself, but because of a not too edifying position in medicine in general. Be that as it may "stomach specialists" were taboo—"villains, vipers, damned without redemption," to use the words of Shakespeare, and the specialty of gastro-enterology, despite the eminence of the men who were trying to develop it, had to struggle for many years to attain a position of dignity and respectability within the profession. That it has succeeded may be attributed in great measure to the achievements of members of this Association. Recognition of the importance of the specialty of gastro-enterology is attested by the fact that the American Board of Internal Medicine has approved a Board of Gastro-Enterology, the members of which it has been the privilege of your Association to name. Credit for the development of this Board largely belongs to Dr. Andresen and his co-members, Drs. Eusterman and Bockus. As long as the destiny of the Board lies in the hands of men such as these—and it is the duty of this Association to see that it does—gastro-enterology will continue to take on new and greater eminence and

the objective of our founder members to promote all that appertains to diseases of the digestive tract will be efficiently served.

From what I have said thus far it should be clear that your Association has met the challenge of the past in a satisfactory manner. But what of the challenge of the future—the challenge hurled at us by this war—the "War for Freedom!" How is this to be met, first in the interests of our country and secondly, in the interests of gastro-enterology! It is first being met by those members of our Association who have been called to the colors in a military and advisory capacity. Well may we be proud of the splendid and unstinted service they are rendering their country. Next I may say the American Gastro-Enterological Association was prompt in offering its services to the military authorities both before and after hostilities began. In June, 1940, the Surgeon General of the War Department expressed his appreciation of the resolution of the Association in placing its services at his disposal. Again in January, 1942, the Surgeon General's office acknowledged the offer of assistance on the part of the Association in dealing with problems pertaining to gastro-enterology, and again expressed great appreciation.

In June, 1940, the Committee on Military Preparedness was appointed by President Ivy. Since that time, this committee has been in frequent correspondence with the Surgeon General's office and appears to have been of great assistance in the development and organization of the specialty of gastro-enterology during the present war. Whatever influence your committee may have had in assisting the Surgeon General's office has been due to the untiring and very capable efforts of its chairman, Dr. Kantor, who holds the rank of Colonel in the Army Medical Reserve Corps. As a result of Dr. Kantor's knowledge and experience in medical reserve corps matters, his advice has been sought on medical problems, and perhaps more to him than anyone else should go the credit for official recognition of the specialty of gastro-enterology by the War Department. As a result of this, a Section of Gastro-Enterology was authorized by the War Department in July, 1940, for all war-time hospitals. The War Department furthermore adopted the policy of placing a gastro-enterologist on the staff of each of the general hospitals and in station hospitals of 800 bed capacity and over. Your committee on military preparedness, in addition to its other duties, has been actively interested in determining the status of chronic gastritis in this war. With the collaboration of Dr. Chevalier Jackson, Dr. H. J. Moersch and Dr. Rudolf Schindler, it submitted to the Surgeon General's office a list of qualified gastroscopists, who it is believed will be of great assistance in this matter.

That the appointment of specialists in gastro-enterology will prove to be of immeasurable benefit to the military service may be gathered from the fact that diseases of the digestive tract in the present war occupy first place, and by a wide margin, as a cause of disability in the armed forces of the allied nations. In the first World War such diseases, according to the statistics of the Surgeon General's office, were listed in no higher than seventh place. It is worthy of particular comment that peptic ulcer, especially of the duodenum, is the main reason for the high rate of disability today.



It is not within the province of this address to do more than comment on the exceedingly interesting and important observations that are being recorded on peptic ulcer, especially by one of our honorary members, Sir Arthur Hurst. Whether the observations will be supported by the facts, accumulated as time goes on, remains to be seen. The reasons for what appears to be an extraordinary increase in the incidence of peptic ulcer offers a challenge of the first magnitude and it clearly becomes the responsibility of the gastro-enterologist to provide the solution for such a surprising and important turn of events. It is hoped that it will be he who will make a critical study of this as well as other diseases of the digestive tract that are being encountered in this war and that he will be able to clarify many of the perplexing aspects of such diseases as gastritis, catarrhal jaundice, acute cholecystitis, dysentery and colitis, to say nothing of such fundamental conditions as nutrition and functional derangements. The interesting symposium held on these subjects at the opening session of this meeting demonstrates that the members of your Association are on the alert, and the character of their presentations presages a position of distinction and influence for gastro-enterology in the military services.

Unparalleled opportunity for clinical research will be provided by this war and as the Army Medical Service rose to high stature during the last war, so can gastro-enterology come into its own during the present war.

To be able to accept the challenge, however, that this war will present, and emerge from it with observations of merit, will require of a man no little training and experience. It therefore becomes the responsibility of the members of the American Gastro-Enterological Association to do all in their power, both collectively and individually, to see that proper facilities and adequate training are provided in the specialty of gastro-enterology. At the present moment the opportunities for one to secure the kind of training in gastro-enterology that will be required for certification in the specialty are woefully inadequate and it is greatly to the credit of the relatively few good clinics and the physicians in charge of them that they have so well met the demands that have been placed upon them. In the future, still more will be expected of them for it will no longer be sufficient to allow for instruction in the sciences alone, formidable as that has become. Psycho-somatic medicine for instance, to which I have referred, is taking its place in the front ranks of our profession and proper recognition and provision for training and instruction in this field will become imperative. Fortunate in this regard will be the physician who through either natural endowment or acquired training, if the latter be possible, is well versed in the art of medicine. Medicine itself is defined as "the healing art" and any course of instruction that permits indifference to this aspect of it is hindering its full development. Furthermore it would well become this Association to find means for the establishment of fellowships in gastro-enterology in appropriate centers.

Research should and must go on, but the ends will

better justify the means—it has been said we are strong on means but weak on ends—when it is better organized and when it functions as a complement and not an eclipse to clinical medicine. Both experimental and clinical research need an organization of the type that H. G. Wells would have for the world at large that "accumulates, sorts, keeps in order and renders available everything that is known." Research and clinical medicine should be tempered, one to the other; and always, no matter what the problem might be, fuller comprehension of it by those with the proper logical equipment must be secured. Complete understanding of any problem in medicine is necessarily dependent on what is known by those in the general practice of medicine. This being the case, it becomes obvious that the white-robed priests may profit by mingling with and taking heed of the potentialities of the general practitioner. Let it be hoped some means may be found to properly organize and utilize the vast clinical experience of those physicians who are not on the staffs of our teaching hospitals or members of our research units. Be it remembered that great truths may be the reward of simple methods and while all respect is due the scientist, it is well to appreciate that "the language of truth is simple" and the deductions of super-statisticians and algebraic equations do not necessarily signify finality in problems medical. There can be no priorities in medicine and to quote from a recent editorial in the *Lancet*: "Intellectual snobbishness, reliance on experts and the fear of doing simple things might well be added to the contraband of war." In harmony with this, may I venture to say that no longer need he who is unadorned with high power be ashamed of his talents, nor he who is unfamiliar with technical procedures and high-sounding phrases remain unaware of his worth, for only through unrestrained professional fellowship and a fraternal blending of opinion can medicine atone for its failures of the past and avoid the pitfalls of the future.

With these comments I would close my address on a wistful note. Looking ahead need not be like peering into an old fashioned kaleidoscope, with the colors not so bright. It is true, the sights are bewildering, the picture confusing, but there must be no room for fears and doubts. The pattern of medicine will change as all man-made things will change, but the change may be wholesome. Let us believe there is a plan and a purpose in what is ordained for us which it behooves us to meet courageously and with good faith—for "only faith can deal with days like these—faith which is both a gift of God and a law of the soul."

The physician, especially he in the spring-tide of life, like the soldier, will meet the challenge of this war as he has met the challenge of all other wars. He will share its fortunes, be they good or bad, in common with the soldier, and to the one as well as the other, I would commend the words of Emerson, dedicated to those young "who hazard all in Freedom's fight"—

"So nigh is grandeur to our dust.

So near is God to man,

When duty whispers low, Thou must,

The youth replies, I can."

# Peptic Ulcer and Irritable Colon in the Army

By

DONALD T. CHAMBERLIN, M.D.\*  
ATLANTA, GEORGIA

THE proper title of this paper should be—Peptic Ulcer and Functional Digestive Disease in an Army General Hospital. Its purpose is to show what has happened during the first months of mobilization. A general hospital is designed to serve general and special, rather than local and ordinary needs. It affords better facilities for the observation and treatment of serious and complicated cases, than can be provided at the ordinary station hospital. It also studies and finally disposes of cases that may have long resisted treatment elsewhere, and gives definitive treatment to patients from hospitals in the theatre of operations (5.) From this explanation of the function of an Army general hospital, it may be seen that by the time a patient reaches a general hospital he has usually had routine studies elsewhere, and in the opinion of the referring medical officer is not responding to treatment, or requires longer treatment than he is authorized to give. In other words, a general hospital is the last stop, and very few patients return to full duty once they are admitted.

The figures presented show the results of the weeding out process which began with the first day of the draft in October, 1940, and still continues. We have been fortunate indeed to have had this interval and not to have been forced to send individuals into combat, where they would have become casualties as inevitably as though they had stopped lead.

These figures also establish a base line in the consideration of digestive disease in military service since the majority of the patients had symptoms prior to induction. It is important to realize that these are civilian rather than military casualties. However, it is notable how closely they resemble the statistics in the British literature in the past year or two, and it may be that actual combat conditions will not increase the incidence of peptic ulcer any more rapidly than it has been increasing in civilian life in the recent past. Probably the incidence of chronic functional digestive disease will increase in proportion as more and more soldiers serve under combat conditions.

A large number of our patients gave their Induction Boards history or other evidence of chronic digestive disease of many year's duration. Other patients were inducted even though they bore the operative scar of repair of a perforated ulcer. Just why this condition existed was not clear, until it developed that early in the draft proceedings no provision was made for study or any hospitalization of inductees to prove or disprove their statements. A rough guide as to a candidate's suitability was set up by many draft boards. If a man had been able to hold a job consistently for the two years previously, he would be able to tolerate army life. The one fact that the Boards forgot, was that in the army an individual is not able to choose

his diet, but must eat in the general mess. The army diet is good, well prepared, well balanced, and far better in quality and quantity than the diets that a large number of the inductees had ever had in their lives. However, it is not a diet designed for special needs, and no provision is made for a wide variety of choices at any one meal. Consequently, the ulcer patients who had been asymptomatic, and many others with functional dyspepsia, began to have increasing digestive difficulty.

Lawson General Hospital admitted its first patients August 1, 1941. During the period, August 1, 1941-May 1, 1942, there were 3492 admissions to the hospital. Of these 1755 were medical patients. Nine per cent of the total hospital admissions or eighteen per cent of all patients admitted with non-surgical conditions were admitted to the Gastro-Intestinal Section. The total number of admissions on the section was 316. Of these 98 or 31% had proven peptic ulcer—80

TABLE I  
*Lawson General Hospital*

|  |           |
|--|-----------|
| Total number admissions October 1, 1941-May 1, 1942  | 3492      |
| Total number admissions to Medical Service           | 1755      |
| Total number admissions to Gastro-Intestinal Section | 316       |
| Number with Peptic Ulcer                             | 98 or 31% |
| Number with Gastric Ulcer                            | 3         |
| Number with Duodenal Ulcer                           | 95        |
| Number with Functional Digestive Disease             | 113       |

enlisted men out of a total of 269, and 18 officers out of a total of 47. Of the enlisted men 77 had duodenal ulcer and 3 gastric ulcer. All the officers save one had duodenal ulcer: and the other had a gastrojejunal ulcer following a pylorotomy and gastro-enterostomy done in 1925. These figures closely approximate the reports from the British with one notable exception—the incidence of gastric ulcer. Willcox (4) reported 41 cases of digestive disease among whom 19 had duodenal ulcer and 7 gastric ulcer. Graham (2) reported 158 cases of peptic ulcer with 135 in the duodenum and 23 in the stomach. Hurst (3) reported 205 cases of which 164 were duodenal and 41 gastric. This incidence of gastric ulcer seems unusually high for this age group especially in view of our figures of 3 gastric ulcers and 95 duodenal ulcer out of a group of 98. Possibly this incidence will change under actual war conditions. We can only wait and see what the convoys bring back to us from overseas.

The enlisted patients with peptic ulcer fall into two fairly well defined groups. First, the older men in service—the professional soldiers—those who enlisted before October 1, 1940, and second, those who were drafted or volunteered after October 1, 1940. In the first group there were 21, several of whom had had more than 20 years' service, and who because of ability and length of service had been eating apart from their

\*Chief Gastro-Intestinal Section, Lawson General Hospital, Atlanta, Georgia.  
Major, Medical Corps, Army of the United States.

organizations for many years. Their length of service varied from 13 months to 23 years. The average age of this group was 28.5 years. When these men went on maneuvers in the fall of 1941 they had recurrences of ulcer manifestations which required their hospitalization. Eight, all of whom were over 30, had their first symptoms at this time. Only two of the group

TABLE II  
*Peptic ulcer*

|   |            |
|---|------------|
| Patients who had enlisted prior to October 1, 1940.                         |            |
| Total number  | 21         |
| Length of service—13 months to 23 years                                     |            |
| Average Age   | 28.5 years |
| Line of Duty—Yes  | 15         |
| Symptoms existed prior to enlistment  | 2          |
| First symptoms in Fall Maneuvers, 1941                                      | 8          |
| Patients drafted or volunteered after October 1, 1941                       |            |
| Total number  | 39         |
| Average length of service—5 months  |            |
| Average Age   | 26.9 years |
| Symptoms existed prior to enlistment  | 31         |
| Line of Duty—Yes  | 2          |
| Knew of presence of ulcer before enlistment                                 | 12         |
| No knowledge of ulcer before enlistment                                     | 72         |
| Additional patients with symptoms on whom diagnosis was not proven by X-ray | 5          |

had symptoms prior to enlistment. The other nineteen were in line of duty.

The second group consisted of 59 enlisted men whose length of service before hospitalization varied from five days to twelve months. The average length of service was five months, and the average age 26.9 years. Of this group all except eight had had their symptoms prior to enlistment and were not considered in line of duty. Three of the eight experienced perforation without previous symptoms while on duty. Nineteen patients presented evidence of peptic ulcer to their induction boards but were drafted in spite of this obstacle. It is doubtful that this will happen again under the present set-up where adequate facilities for checking diagnoses now exist. The remaining 32 patients, who had histories suggestive of ulcer, had never been studied previously and had no knowledge of the existence of ulcer. The average duration of symptoms prior to induction in this group was two

TABLE III

|                           |    |
|---------------------------|----|
| Officers                  | 47 |
| With Peptic Ulcer         | 18 |
| Disposition—              |    |
| Limited Duty              | 2  |
| Retired                   | 16 |
| With Functional Disorders | 15 |
| Disposition—              |    |
| Duty                      | 11 |
| Retired                   | 4  |
| Diagnoses—                |    |
| Hyperchlorhydria          | 3  |
| Hypertrophic Gastritis    | 1  |
| Irritable Colon           | 11 |

and one-half years and varied from one to twenty years.

There was an additional small group of eight patients on whom the diagnosis of peptic ulcer was not proven by X-ray, but who had typical histories and high free gastric acidity. Five of this group had been on duty for one month before hospitalization; two, two months and one each, three and four months

respectively. These men were all discharged on certificates of physical disability with the diagnosis of hyperchlorhydria. There is considerable reason to believe that these men all had duodenal ulcer, although we were unable to prove it by X-ray.

The officer patients with ulcer presented a problem of disposition which often was not pleasant, particularly with some of the regular army officers who bitterly fought retirement, especially at this time. In general this attitude was taken by all the officers who had to be retired or returned to inactive status as in the case of Reserve and National Guard Officers. Most of these officers were keen and valuable men whose change in status constituted a serious loss to the service. Unfortunately the category of limited service does not fit this situation since it is impossible to assure them permanency in a position where they can control their diets. Out of the fifteen only two were sent to limited duty in positions where their hours are regular and where their diets may be controlled. The other sixteen officers were either retired, in the case of the Regular Army or sent to inactive duty in the case of the Reserves. One is torn between the desire to be a good fellow and return an officer to full duty, and the knowledge that he will inevitably break down again in a few days or months in the field. However one must be realistic, uncompromising and avoid indulgence in wishful thinking when dealing with such individuals. One should not allow oneself to be swayed

TABLE IV

|                      |     |
|----------------------|-----|
| Functional           |     |
| Total number         |     |
| Enlisted men         | 113 |
| Officers             | 15  |
| Discharged, C. D. D. | 76  |
| Duty                 | 47  |
| Retired              | 4   |

by pleas, or plans evolved for temporary care of the diet. Conditions are such and events occurring so rapidly that no one on full duty may be assured of a permanent position or station. Without such assurance it is not safe for an ulcer patient to be on duty. It has been suggested that as the need for man-power increases, patients with ulcer may be utilized in the service. In our opinion this is a dangerous precept since the symptoms will inevitably recur. These men will take beds, and the attention of medical officers, badly needed for actual battle casualties. The ulcer patient can do his part in civil life where he can better regulate his hours and his diet. His place is there and not in the service.

One hundred thirteen enlisted patients and fifteen officers were admitted for functional disorders, principally irritable colon. Early in the year the problem of the disposition of these individuals arose. After the procedure of reclassification for enlisted men was instituted, it was thought by some, that these men could be transferred to training or labor battalions and function adequately. However, it soon became apparent that such was not the case, since in any organization these men would have to eat in a general mess. The same conditions would pertain that had been present previously, and which had contributed to their hospitalization. In this group, as in the ulcer group, were many who had done well in civil life so

long as they could control their diets. When confronted with prescribed meals and while on maneuvers, irregular meals, hastily prepared, began having crippling symptoms which necessitated their hospitalization. The psychic factors involved in these cases vary from simple dislike of the service through difficult adjustments to the life, to true psychoses. The true psychotics were usually seen, and disposed of, by the Neuropsychiatric Service. As many of the rest as possible were seen by that service, to rule out underlying psychoses, and for psychotherapy. The latter procedure has not been very successful since usually all that can be offered is a suggestion of change of environment. This is done when the patients reach the hospital where usually, with proper dietary care these individuals become symptom free. Our procedure in many cases where all symptoms have subsided, is to send the patient to the general mess. If he finds he can tolerate this diet for a week, he is then considered fit for duty and sent back to his organization. No patient is returned to duty who cannot tolerate the regular diet in the mess hall, going through the line and eating with his fellow patients.

Of the group of 113 enlisted personnel, 76 were discharged on certificate of physical disability with the diagnosis of Intestinal Indigestion. This diagnosis is not satisfactory in that it does not name the specific mal-function involved in each particular case, but it is the best we could find for the functional cases. The diagnosis of Irritable Colon is not included in the Army Diagnostic Table. It is not considered proper to use the nomenclature of inflammatory disease, such as colitis or gastritis, where no evidence of inflammation other than symptoms may be found, even though these are qualified by the words spastic or some other equivocal adjective.

Thirty-seven cases were returned to duty, who after periods of treatment varying from two weeks to three months, became symptom free and able to tolerate the general mess. These patients, it was felt, would be able to carry on without further hospitalization for their digestive symptoms.

TABLE V

|  |    |
|--|----|
| Miscellaneous Diagnoses on Gastro-Intestinal Section | 56 |
| Cardio-palm  | 2  |
| Catarrhal Jaundice                                   | 4  |
| Hookworm Infestation                                 | 15 |
| Cholelithiasis                                       | 5  |
| Ulcerative Colitis                                   | 2  |
| Diverticulitis of Sigmoid                            | 1  |
| Amoebic Dysentery                                    | 1  |
| Bacillary Dysentery                                  | 4  |
| Acute gastro-enteritis (post alcoholic)              | 14 |
| Cirrhosis of the Liver                               | 1  |
| Carcinoma of the Stomach                             | 2  |
| Hemorrhoids  | 2  |

The fifteen officers grouped in this classification had the following conditions: Hyperchlorhydria 3, Hypertrophic Gastritis 1, Irritable Colon 11. The first four were sent to duty, but of the group of eleven with irritable colon there were four who had such acute diarrhea, if they made the slightest deviation from their diets, that they were placed on an inactive status. The remaining seven returned to duty. Only one was re-admitted from this group with a recurrence. The psychic factors played a more prominent role among

these officers than in any other group. They all gave a history of digestive unrest increasing as the burden of responsibility increased, until finally they required hospitalization for relief.

The remaining 56 cases on the section were the ordinary conditions seen in a civilian practice, and were treated as required. Their treatment and disposition presented no unusual problems and consideration of this group is not relevant to the purpose of this paper. The figures are shown only for the sake of completeness.

TABLE VI

*Data from Tilton General Hospital, Fort Dix, New Jersey (Lt. J. Edward Berk)*

|   |     |
|---|-----|
| Admissions to G. I. Section, October 1, 1941-March 15, 1942 | 113 |
| Peptic Ulcer  | 49  |
| Gastric Ulcer   | 2   |
| Duodenal Ulcer  | 47  |
| Discharged on C. D. D.                                      | 41  |
| Limited Duty  | 2   |
| Duty  | 4   |
| Retired   | 2   |
| Average length of service—4½ months                         |     |
| Knew they had ulcer   | 13  |

Lieutenant J. Edward Berk, Chief of the Gastro-Intestinal Section at Tilton General Hospital, Fort Dix, New Jersey, and his associate Lieutenant George C. Brady were kind enough to send me an excellent summary of their statistics on peptic ulcer at their station. They selected the period October 1, 1941, when the hospital opened, to March 15, 1942. During this time there were one hundred thirteen admissions to the Gastro-Intestinal Section. Forty-nine of these had peptic ulcer—two gastric ulcer and forty-seven duodenal ulcer. Forty-one were discharged on certificate of disability, two were retired, four returned to duty, and two to limited duty. Only five had never had symptoms prior to induction, thirteen knew they had ulcer but were accepted in spite of this. The average length of service before hospitalization was four and one-half months, and this varied from one day to fourteen months.

Comment: The statistics of peptic ulcer from two general hospitals are similar. Both report a high incidence of enlisted personnel with ulcer who should not have been in the service. In our opinion, a man with a peptic ulcer is unfit for military service. This has been born out and emphasized by the statistics—the average length of service for the entire group of ulcer patients (147) from the two hospitals was five months. No matter how well these men were before induction, their break-down in the Army was inevitable. The chance that a patient with peptic ulcer may escape disabling symptoms in the service is slight. He is an expense to the government and his induction or commission is unwise in the light of our experience.

The large group with functional digestive disease presents a rather difficult problem. It is not possible to eliminate many of this group at the beginning of their service. They must be observed, studied and the true status of each case evaluated in relation to the military service. The true psychotics, the constitutionally inadequate, and the morons must be weeded out and discharged. The remainder of this group must

be studied as individuals and returned to duty whenever possible.

The low incidence of gastric ulcer (5 out of 147) is probably due to the age group of the patients, since the incidence in the general population varies from 9 to 1 to 4 to 1 duodenal over gastric ulcer, depending on the reviewer (6.) The incidence in the British Army is considerably higher than in our Army to date. This may be due to life in actual combat for a longer time, restricted diets, or other factors at present obscure. Time alone will show the relation of combat to the incidence of gastric ulcer in the American Army.

#### SUMMARY

1. Three hundred and sixteen patients in Lawson General Hospital were admitted to the Gastro-Intestinal Section from August 1, 1941 to May 1, 1942.

2. This represented 9% of the total hospital admissions and 18% of those admitted to the Medical Service.

3. Thirty-one per cent had proven peptic ulcer. These patients averaged five and one-half months service before symptoms became severe enough to require hospitalization.

4. The man with a peptic ulcer is unfit for military service.

5. Statistics from Tilton General Hospital, Fort Dix, New Jersey, are very similar but show a higher incidence of peptic ulcer (49 out of 113 admissions.)

6. The problem of disposition of patients with functional digestive diseases is discussed.

#### BIBLIOGRAPHY

1. Lieutenant J. Edward Berk: Personal communication.
2. Graham, J. G. and Kerr, J. D. O.: "Digestive Disorders in the Forces." *Brit. Med. J.*, 1:473-476, 1941.
3. Hurst, A. F.: "Digestive Disorders in Soldiers." *Am. J. Dig. Dis.*, 8:321-323, Sept., 1911.
4. Wilcox, P. H.: "Gastric Disorders in the Services." *Brit. Med. J.*, 1:1009-1012, 1940.
5. War Department Technical Manual, 8-260. "Fixed Hospitals of the Medical Department." Par. 4, pp. 5-6, July 16, 1941.
6. McNullen, I. W.: A Roentgenographic Study of the Relative Incidence of Gastric and Duodenal Ulcer. *Radiology*, 37:194-196, 1941.

## Diseases of Anorectum and Colon

### Review of Certain Recent Contributions

By

ROBERT TURELL, M.D.  
NEW YORK, NEW YORK

**I**N this review the subject of proctologic disease has been dealt with from a broad point of view. In addition to reemphasizing established principles and procedures, an attempt was made to collect in one place new and important facts in proctology as they have appeared in the literature during the year of 1941. A few important references of the preceding year, which were inadvertently omitted from the last review (1) are also included in this paper.

#### NEOPLASTIC DISEASE

**Polyps:** Kennedy (2) observed polyps of the rectum and colon in 49 infants and children. Bleeding from the rectum was the most common symptom. The diagnosis of polyps was made by proctosigmoidoscopic and roentgenologic means. Practically every accepted method of treatment was utilized in the management of the polyps encountered in this group of patients. Endoscopic fulguration alone was employed in 27 cases; excision alone was practiced in one; ligation was performed twice; transcolonic excision was carried out in 2 instances; fulguration combined with transcolonic excision was performed in 3 patients, and fulguration and segmental resection were resorted to in 2 cases. A comprehensive study of this material convinced Kennedy that adenomatous polyps, excepting some of those found in association with chronic ulcerative colitis, have carcinomatous potentialities, and should therefore be extirpated. This is in agreement with the opinions of other investigators (3, 4, 5, 6, 7, 8, 9.) Green (4) discussed 70 consecutive cases of polyps, which constituted 10.8 per cent of the total number of patients he subjected to sigmoidoscopic ex-

amination. Too much dependence should not be placed on the roentgenologic examination alone because many of the polyps are too small for roentgenologic visualization. In general, neoplasms occurring in the ampulla are especially missed by the Roentgen-ray examination (7.) Jackman (5) reported an instructive case of annular adenocarcinoma of the rectosigmoid, that apparently developed from preexisting benign polyps which had been observed in the rectosigmoid some 6 years previously. Incidentally, fulguration of the polyps had been advised but was refused. Although this report deals with only one case, it nevertheless, shows the consequences of untreated benign adenomas. The reviewer has observed a similar unfortunate case this year.

Polyps occurring in the terminal bowel should be fulgurated endoscopically (6, 10.) A radical operation may be indicated when malignant cells are found near or at the base of the polyp (10, 11.) The advisability of making serial sections of extirpated polyps, especially near the base, is stressed (11.)

Adenomatosis of the colon is regarded as a hereditary and perhaps a congenital disease. Because of the tendency of the adenomas to undergo malignant changes during the early decades of life, diffuse adenomatosis constitutes a surgical problem (12.) Rankin (12) prefers to fulgurate the polyps of the rectum first and then he performs an anastomosis between the ileum and the lowest segment of the sigmoid. The ileosigmoidostomy may be performed in one of 2 ways: (1) aseptic end-to-side anastomosis between the terminal ileum and the lower sigmoid over a Rankin clamp, or (2) with the aid of a Murphy button. In the absence of a malignancy, subsequent



resection of the colon down to the point of anastomosis is usually delayed for several months. Following colectomy, the patient will have 3 or 4 bowel movements per day during the first few months. Subsequently, one or 2 daily movements occur, and the stools usually become semisolid or formed.

*Carcinoma of Anus, Rectum and Colon.* The hereditary factors are discussed by Riemann (7), who believes that only the potency to develop cancer is inheritable, and by Bagen (9), who suggests the existence of a "potentially malignant" state in the tissues of the intestinal wall. "The potentially malignant region is a region in which an inflammatory reaction has led to a disturbance of the normal environmental relation of some of the epithelial cells" (13.) Bagen and his collaborators (13) studied the epithelium surrounding primary colonic cancers and observed multiple mucosal excrescences measuring from 1 to 4 mm. in the diameter as far as 15 cm. away from the site of the neoplasm. There were also noted subepithelial aggregations of lymphocytes of variable sizes, which tended to disrupt the continuity of the muscularis mucosae. These changes were absent in 100 normal (control) colons.

Coller, Kay and MacIntyre (14) presented an instructive paper dealing with the routes of the spread of carcinoma of the colon to the regional lymphatics: this study is similar to their previously published paper dealing with regional lymphatic metastases of carcinoma of the rectum. The size of the lymph nodes is not an index of metastatic involvement: the extent of the lymphatic involvement can neither be correlated with the duration of the disease nor with the size of neoplasm. The operative procedure should be planned on anatomic basis in order to include all lymph node bearing areas.

Lawrence (15) discussed basal cell epithelioma of the anus and added 2 cases to the 4 which had been recorded in the literature. The large sized tumors are treated by posterior resection of the anorectum with or without post-operative irradiation, while the smaller lesions are treated by radium and irradiation. Because basal cell carcinoma in other parts of the body rarely, if ever, metastasizes to lymph nodes, Lawrence questions the occurrence of metastases in basal cell carcinoma involving the anus. Hence there is hardly an indication for a radical procedure, such as an abdominoperineal resection which is the proper treatment for epidermoid cancer of the anal region. Harris (16) discussed his experience with squamous cell carcinoma of the anal canal. He believes that irradiation is apparently the treatment of choice. Hayes and Burr (11) employed fulguration in the treatment of an inoperable case of squamous cell carcinoma. In some cases the combination of irradiation and fulguration has advantages over either form of therapy when used alone (17.)

Hayes and Burr (11) encountered a case of colloid (mucinous) carcinoma which originated in an anal fistula. The possible relationship of untreated inflammatory or other benign anal lesions to the development of anal neoplasm has long ago been dealt with by Curtice Rosser.

The diagnostic importance of digital exploration and sigmoidoscopy in carcinoma of the rectum is empha-

sized by Mayo (17.) He believes that digital examination is especially useful in establishing the degree of fixation of the lesion. Lesions graded as "mobile" or "moderately mobile" are regarded as operable, while those graded as "fixed" or "moderately fixed" suggest questionable operability; an exploratory laparotomy is indicated in these cases. Case (18) believes that digital examination of the rectum and sigmoidoscopy should invariably precede the Roentgen-ray examination of the colon with the aid of opaque enemas. "The roentgenological detection of colonic neoplasm depends upon some alteration of the bowel wall, affecting its lumen or its elasticity, which can be recognized as more or less of a filling defect, perhaps involving the mucosal pattern, but more likely, when discovered, to have already invaded the submucous and muscular layers" (18.) Gershon-Cohen and Shay (19) stated that the double contrast enema reveals early carcinoma of the colon before subjective symptoms have occurred.

The value of preliminary biopsies has been emphasized by most writers. Hartzell (20) cautions against the fallacy of removing the piled-up mucosa which is present along the border of the neoplasm for histologic studies, and he furthermore stresses the importance of repeated biopsies.

Buirge (21) believes that the early symptoms of malignant disease of the colon are not yet sufficiently well understood by both the patient and the physician. He stated that bleeding did not occur in 8.6 per cent of his cases; that 9.4 per cent of the patients had had associated hemorrhoids, and that less than one-half (48 per cent) of 119 rectal cancers were correctly diagnosed. McLaughlin and Dilworth (22) condemned the pernicious practice of treating hemorrhoids without a thorough sigmoidoscopic study. The practice of ascribing bleeding from the rectum to hemorrhoids is to be deplored. The responsibility of early diagnosis of cancer of the anorectum still rests with the general practitioner (23.)

The significance of extrarectal masses in the rectovesical space was discussed by Buie, Jackman and Vickers (24.) The extrarectal masses may originate in lesions of the genital or gastro-intestinal tracts, but may cause symptoms referable to the rectum, simulating rectal malignancies.

The operability rate of cancer of the rectum in 1186 patients was analyzed by Goligher (25.) This study disclosed an operability rate of 64.5 per cent for women and of 58.5 per cent for men. Inoperability was due to the advanced state of the growth in 32 per cent while in 8 per cent inoperability was due to the poor general health of the patient. Inoperability of the neoplasm proper was determined by one or more of the following conditions: (1) local fixation of the growth; (2) hepatic metastases; (3) peritoneal malignant plaques, and (4) extensive involvement of the abdominal regional lymph nodes. The operability rate was highest between the ages of 40 and 49 years. Johnson and Lombard (26) studied the operative mortality of patients with cancer in general and concluded that the age of the patient and the length of the operation are of utmost importance, with the latter perhaps the more significant of these two factors.

While it is generally conceded that no single oper-



ation will fit to the needs of every patient, there, nevertheless, exists considerable unanimity of opinion that the one-stage abdominoperineal resection of the rectum as conceived and described by Miles, is the operation of choice for the extirpation of malignancies of the rectum and rectosigmoid. Mayo (17) reported a mortality rate of only 5.5 per cent following 144 consecutive one-stage Miles procedures; not a single death occurred in the last 74 consecutive operations performed by him. This is indeed a remarkable record! Singleton (23) described his experiences with the performance of the perineal-abdominal operation for carcinoma of the rectum. This operation is more frequently performed in Great Britain than in the United States. Occasionally, resection of the rectosigmoid with end-to-end anastomosis of the sigmoid to the rectum with preservation of the anal sphincters (Dixon) is practiced (27.) Hogeboom (28) favors a preliminary Devine type of colostomy to resection of the pelvic colon or rectosigmoid for carcinoma. A severe hemorrhage occurring after the crushing of the spur of the Devine type of colostomy has recently been reported (11.) It is questionable whether the results of resection of the rectosigmoid with end-to-end anastomosis with preservation of the rectum and anal sphincters will statistically compare with those following the radical abdominoperineal procedure.

Gregg and Dixon (29) stated that primary resection of malignant lesions of the colon should not be attempted in the presence of acute obstruction; preliminary cecostomy or colostomy is always advisable. The ultimate prognosis for patients who have carcinoma of the colon which produces obstruction is definitely worse than for those patients who do not have this complication. Gibbon and Hodge (30) feel that in the hands of the general surgeon, resection with an aseptic, immediate anastomosis preceded by decompression (cecostomy or colostomy) is the operation of choice for carcinoma of the colon. Koster (31) presented a method of exteriorizing the anastomosis after colonic resection and closing the wound around it; this method is believed to prevent or diminish peritonitis from leakage.

Surgical diathermy is of definite value as a palliative procedure in the management of inoperable carcinoma of the rectum, and as a curative procedure in the occasional case of fungating cancer where operation appears to be contraindicated (32.) In operable cases, surgical diathermy may be curative for the papillary malignant lesion without involvement of the base (11) or of the submucosal tissues. Electrocoagulation is also useful for the treatment of operable rectal cancers in patients who cannot withstand an operable procedure. In certain cases, irradiation and radium therapy may be advantageously combined with surgical diathermy; these are complementary and not competitive measures (33.)

The palliative value of irradiation alone has not yet been determined (7.) However, Roberts (34) believes that irradiation of inoperable cancer of the rectum provides a method of restoring rectal function to a degree compatible with an active life for a certain period of time; apparently irradiation does not influence the length of survival but it does increase the

well-being of the patient during the period of survival.

The prognosis of carcinoma of the terminal bowel is still difficult to estimate. In general, the prognosis depends on the age of the patient; the duration of symptoms; the size of the neoplasm; the histologic pattern, and metastasis to the regional lymph nodes (35, 36.) Papillary neoplasms have a distinctly better prognosis than the infiltrating tumors. A patient surviving 5 years or more from resection of a primary adenocarcinoma of the rectum may apparently be regarded as "cured" (36.)

The present day superior results following colonic and major rectal surgery are largely due to various operative technical refinements; the frequent transfusion of blood; the restoration of the normal balance of fluid, electrolytes and protein, and the administration of vitamins and other essential substances of which the body may be deficient or depleted. Mayo (17) still advocates pre-operative peritoneal injections of vaccine to help prevent post-operative peritonitis. The value of the pre-operative and post-operative administration of the sulfonamides in the prevention of peritonitis has been studied extensively (37, 38, 39.) The sulfonamide compounds deposited in the peritoneal cavity and in the wounds at the conclusion of an operative procedure have real merit (40, 41.) The augmentation of the local cellular defense mechanism produced by the intraperitoneally deposited sulfonamides is similar to that of intraperitoneal vaccination (37.) The coliform flora of the large bowel can usually be significantly reduced by the adequate administration of sulfaguanidine. However, no such reduction in the number of the coliform organisms is possible in the presence of ulcerative lesions of the colon (42); nor has sulfaguanidine any therapeutic value in experimental *B. coli* peritonitis (43.)

Spinal anesthesia using procaine hydrochloride appears to be the anesthetic of choice for colonic and major rectal surgery. Mayo (17) combines spinal anesthesia with the intravenous administration of pentothal sodium; he has also employed continuous spinal anesthesia. Hayes and Burr (11) and Wilcox (44) prefer pontocaine for spinal anesthesia.

*Urogenital Complications of Malignant Disease of the Colon and Rectum:* Two papers by Seaman and Binnig (45) and Ewert (46) on urologic complications following colonic and major rectal surgery are worthy of special comment. Urologic complications are either the result of the neoplasm in the terminal bowel or of the operative procedure employed for the extirpation of the new growth. The urinary complications vary in occurrence and severity, and are frequently due to destruction or trauma of the sympathetic and parasympathetic nerves, and possibly also to infection. Infection is a common accompaniment probably because of the neural disturbances and the altered position of the base of the bladder. Hence, infection should be interrelated with the neuromuscular vesical physiology in some cases at least. Bladder paralysis must be handled properly in order to avoid irreparable damage to the upper urinary tract. The duration of the urinary disturbances depends upon the extent and character of the neural injuries.

*Management of Colostomy:* Adjustment to permanent colostomy is frequently difficult and, at times,

almost impossible in the occasional patient who is considered psychologically unfitted to tolerate an artificial abdominal anus. Smith (47) and Jennings (48) contributed timely papers dealing with the management of colostomies.

*Benign Lesions Simulating Carcinoma of Colon or Rectum:* Hunt (49) discussed the various manifestations of hemangiomas of the colon and rectum. He believes that extensive intramural hemangiomas of the colon and rectum require radical extirpation of the involved segment of the intestine. An extensive hemangioma involving the rectum and rectosigmoid was successfully eradicated by an abdominoperineal resection.

Barlow (50) stated that simple nonspecific ulceration of the cecum, colon and rectum is a clinical entity, and that pathologically it resembles the ulcerations of the stomach and duodenum. This lesion is almost never diagnosed prior to operation or necropsy; only one ulcer, that of the rectum, was correctly diagnosed on biopsy. A study of the literature revealed that 66 per cent of the ulcers in the right colon and 81 per cent of the ulcers in the left colon were already perforated when first seen. In these cases, vague or no symptoms existed before perforation. A further 10 per cent of ulcers in the sigmoid were reported as on the point of perforating; most of these patients had had acute localized pain. The treatment is surgical; the choice of operative procedure depends on the site, virulence, stage of the disease and the state of the bowel wall.

Gault and Kaplan (51) reviewed the literature and reported a personal case of lipoma of the colon which is a rare lesion. Lipoma of the colon is seldom diagnosed before operation because of its occurrence during the so-called cancer age; the similarity of the symptoms, especially when acute, to those of obstruction due to carcinoma, and the absence of a characteristic defect to roentgenologic examination. Kantor (52) has recently observed a submucous lipoma of the rectum.

Endometriosis of the colon and rectum may be either symptomless or productive of a variety of symptoms including acute obstruction which simulates that produced by carcinoma. Usually endometriomas of the colon regress following castration or following castration combined with the performance of a colostomy for obstruction. Occasionally, resection of the involved segment of the colon is indicated. Patton and Patton (53) reported 2 cases of endometriosis of the colon which required resection of the involved segment of the bowel. Curiously in both patients invasion of the mucosa by endometriosis was demonstrated histologically.

Colp contributed an instructive and extremely important paper on colonic spasm as a cause of intestinal obstruction (54.) He discussed in detail 5 cases of obstruction of the colon in which a pre-operative diagnosis of a neoplasm was made but in which subsequent events led to the correct diagnosis of muscular spasm as the cause of the obstruction. In addition to the detailed discussion of his own cases, Colp abstracted briefly the cases reported in the literature. Muscular contraction appeared to be localized to a small area of the large intestine. Occasionally, the spastic segment of the colon was palpated as a firm mass. The patients

never appeared acutely ill. The characteristic fluoroscopic and roentgenologic findings are different from those seen in colonic malignancies. Treatment of these cases consists of that usually accorded any patient suffering from an acute intestinal obstruction. Following surgical intervention, these spasmodic episodes have not recurred.

#### DIVERTICULOSIS AND DIVERTICULITIS

Walking (55) regards acute diverticulitis as a medical problem until complications arise. Most patients recover without surgical intervention. The simplest surgical procedures should be utilized in the treatment of surgical complications. Eggers (56) reviewed his observations of 82 private and clinic patients with diverticulitis. All but 3 colostomized patients had been observed as primary cases during the acute stage. Most of these patients recovered under conservative medical therapy. A number of recurrences took place, and these convinced Eggers that there is no positive safeguard against acute inflammation in diverticulosis. The complications of diverticulitis requiring surgical intervention are emphasized. Babcock (57) believes that medical treatment for diverticulitis affords symptomatic relief only; it is neither corrective nor does it eliminate the possible complications. No important advances can be expected from medical measures alone. Babcock believes that the present mortality and morbidity of diverticulitis bring to mind the mid-Victorian period in appendicitis. Radical surgery for the early stages of diverticulitis is curative and attended by a lower mortality. For the present a modified Paul type of sigmoidectomy is suggested.

#### DIARRHEAS

*Experimental Considerations:* Lium (58) produced diarrhea and increased motor activity of the rectum, accompanied by mucus and blood, by the experimental removal of the celiac and the superior and inferior mesenteric ganglia of dogs. His studies suggest that either hypoactivity of the sympathetic or hyperactivity of the parasympathetic nerves may produce profound motor and structural intestinal changes in dogs. That similar neural influences are at play in human beings is implied but not proved (Hurst.) Poppe (59) was able to produce acute and chronic enteritis with ulceration of the mucosa of the colon by obstructing the lymphatic drainage of the ileocecal segment of the intestine of dogs.

Bercovitz (60) emphasized that the presence of cellular exudates in the bowel discharges is indicative of pathologic changes of the intestinal mucosa. By means of this simple test, diarrhea of functional or nervous origin may be easily distinguished from that caused by organic colonic lesions. Four main types of cells may be encountered: (1) epithelial cells; (2) polymorphonuclear leukocytes; (3) round cells, and (4) macrophages. In amebic dysentery a scanty cellular exudate is discernible while in bacillary dysentery the cellular exudate is profuse with an abundance of endothelial macrophages which resemble free-resting amebae with which they may be confused.

*Chronic Ulcerative Colitis:* The etiology of this lesion is still undetermined; it probably is a syndrome due to one or more still unknown factors (61.) Dack (62) and his associates believe that *B. necrophorum*,

a non-sporulating anaerobe, together with additional still poorly understood factors, plays an etiologic role in chronic ulcerative colitis. The etiologic importance of fungi and monilia was studied by Swartz and Jankelson (63.) They demonstrated an abundance of comparatively pure cultures of *mycoderma geotrichum* in the stools of 87.5 per cent of patients suffering from chronic ulcerative colitis, while in 33.3 per cent of normal controls only scant colonies of similar organisms were grown. In addition, *monilia albicans* were found in 3 patients with a fulminating type of acute ulcerative colitis.

The surgical treatment of chronic ulcerative colitis has recently received extensive consideration (62, 64, 65, 66, 67.) It has been established that appendicectomy and cecostomy are of no therapeutic value; incidentally, these procedures are still in vogue in Great Britain. Ileostomy is carried out when medical treatment is failing or in the acute fulminating cases. Ileostomy is as useless for complicating hemorrhage (65, 67) as gastro-enterostomy is for the control of bleeding from peptic ulcer (65.) Stone believes that an ileostomy performed early in the course of the disease may bring about complete healing of the colon or may prevent the late sequelae. Lahey has endorsed this idea (68.) Ileostomy as practiced now produces marked improvement in the general health of the patient without materially affecting the course of the colonic lesion. Colectomy in graded operations is usually required. Following colectomy, the ileum assumes the function of the colon (65, 69.) Garlock (66) is conducting an interesting clinical experiment: Unless severely involved by perirectal suppurations and fistulas, and polypoid degeneration, he preserves the rectum in anticipation of a future ileoproctostomy.

Dragstedt (62) envelops the ileac stoma with a skin graft at the conclusion of the operation in order to eliminate excoriation of the surrounding skin. According to Bancroft (70) a paste made of yeast and applied to the ileac stoma and adjacent skin exerts a similar beneficial effect.

The mortality factors in the surgical treatment of chronic ulcerative colitis are the subject of an instructive paper (67.) Surgery performed too late is considered the primary mortality factor: hemorrhage or peritonitis are the dreaded complications. Peritonitis is decreased or avoided if intraperitoneal exploration and manipulation of the colon are avoided at the time of ileostomy (66), and if the distal stoma of the ileum is exteriorized as a submucous fistula after the performance of the ileostomy. This procedure will avoid "blow outs" of the inverted, sutured stump (66, 67.) The distal divided ends of the colon should be similarly exteriorized. The value of the sulfonamides for the prevention of post-operative peritonitis has been extensively studied (67, 37, 38, 39, 41.)

Elsom and Ferguson (64) reemphasized the advantages of a medico-surgical team for the investigation of patients with chronic ulcerative colitis. These investigators also studied the value of medical and surgical therapy in two comparable groups of patients: one received medical treatment only while the other group received medical treatment followed by accepted surgical therapy. The mortality of these two groups was practically equal. The medically-treated patients had exhibited continued or intermittent manifestations of the disease. In contrast, the

patients who were operated upon had been more nearly restored to health; in most of these instances dramatic recoveries occurred. Most of the surgically treated patients lead, by their own definition, a normal life in spite of the permanent ileostomy.

Renal calculi apparently occur more often among patients suffering from chronic ulcerative colitis who had had an ileostomy without colectomy than in those patients who had not undergone ileostomy (71.) This study appears to emphasize that ileostomy does not "cure" chronic ulcerative colitis and that the renal complications are secondary to the infection still present in the colon.

*Bacillary Dysentery:* Quinlivan (72) showed that food handlers frequently constitute a dangerous source of bacillary dysentery.

A new culture medium selective for *B. dysenteriae*, Flexner, has been developed (73.) The growth of other enteric organisms, including the Duval-Sonne dysentery bacillus, is suppressed. Cruikshank and Swyer demonstrated that a higher proportion of the Duval-Sonne organisms can be isolated from swabs than from fecal specimens. This applies to all dysentery organisms. Specimens for culture are best secured at the time of proctosigmoidoscopy which should be accorded all patients having diarrhea.

The therapeutic value of the sulfonamide compounds in acute bacillary dysentery has been established. Sulfapyridine (74, 75), sulfathiazole (72, 76, 77, 78) and sulfaguanidine (79, 80, 81) have been employed. Sulfaguanidine, the guanidine analogue of sulfapyridine and sulfathiazole, is water soluble and yet poorly absorbed from the intestinal tract. This permits a high concentration of the drug in the intestine and a low concentration in the blood and body tissues. Sulfaguanidine (and the other sulfonamides) tends to prevent a convalescent carrier state which is present in about 50 per cent of untreated bacteriologically controlled cases (81.)

The value of chemotherapy in the chronic cases and in those with involvement of the submucous structures, the mesenteric lymphatic system and blood stream invasion remains to be assessed.

The prophylactic and therapeutic value of a potent polyvalent mixture of bacteriophage that has been produced from locally obtained strains of dysentery organisms was recently investigated (82.) One group of 113 soldiers who were exposed to bacillary dysentery were given 10 cc. of a bacteriophage polyvalent mixture on 3 successive mornings, while another group of 250 similarly exposed soldiers served as controls. During the succeeding 8 weeks, 10 of the 250 controls manifested dysentery while none of the 113 prophylactically treated soldiers developed the disease. A study of the therapeutic value of the bacteriophage during an epidemic disclosed that the administration of bacteriophage polyvalent mixture was effective in the mild and moderately severe cases of Flexner-Y dysentery. Only occasional improvements and frequent exacerbations were observed in the severe cases of dysentery (the value of bacteriophage therapy in these cases requires further investigation.) In 16 carriers (Flexner), the dysentery organisms disappeared following the administration of the bacteriophage polyvalent mixture on 3 successive days.

The part played by vitamin deficiencies in the production of clinical manifestations of bacillary dysen-

tery is of sufficient interest and importance to warrant an editorial comment in the Journal of the American Medical Association (83.)

The pectins and pectin containing substances are quite widely employed in the treatment of bacillary dysentery. The therapeutic action of the pectins has been studied by various investigators. The "efficiency" of unmodified apple sauce in curing experimental diarrhea in rats was rated at 84 per cent while apple sauce in which the pectins were digested by enzymes showed an efficiency of only 39 per cent (84), thus showing the dominant therapeutic action of the pectins. Pectin is decomposed chiefly in the colon (85.) When given alone, pectins show less decomposition than when added to a mixed diet. Decomposition also depends on the rate of the passage of the pectin through the alimentary tract; the slower the passage the more decomposition occurs. Pectin is completely hydrolyzed by bacterial enzymes (86, 85.)

*Amebic Dysentery:* A simple culture medium for *E. histolytica* was described by Adler and Foner (87.) Snyder and Meleney (88) described a method for obtaining cysts of *E. histolytica* free of living bacteria. Excystation was brought about by methods which caused a decrease of the oxygen tension of the medium. Continued cultivation of the bacteria-free excysted forms was not possible without the addition of living bacteria. Preliminary studies on the development of a culture medium in which *E. histolytica* will grow without bacteria have been described by others (89.)

Faust demonstrated *E. histolytica* within the bowel at necropsy performed within 4 hours after death in 13 out of 202 persons who had died suddenly as a result of an accident. The intestinal lesions of this group of patients were confined to the mucosa and consisted of 3 types: (1) minute pin point lesions; (2) shallow craters, and (3) extensive, superficial erosive lesions. Leukocytic infiltration suggesting secondary invasion by bacteria or of a fibrous process were not discernible (90.)

Johnson (91) made a careful study of 11 monkeys which were carriers of an ameba that is indistinguishable from *E. histolytica* in man. In the absence of symptoms and gross lesions of the infected intestine, invasion of the tissue by the amebae was nevertheless demonstrated microscopically. Because of the possible similarity of amebic infections of monkeys to that of man, this information lends support to the fact that every carrier of *E. histolytica* should be treated as a public health measure as well as for his own future welfare. Apparently, no carrier escapes without some damage to the invaded tissues (91.) This is in agreement with Faust (92) who advocates treatment for amebiasis in the acute, subacute, chronic or carrier states until the patient is definitely freed from *E. histolytica*.

Emetine, contrary to the popular belief, is not curative but is indicated in acute amebiasis only for the control of symptoms (92.) The periodic administration or insufficient dosage of emetine or its compounds should be avoided; such methods of administration may render *E. histolytica* emetine-fast (93.) Chinifon is a potent nontoxic agent and is the drug of choice for the treatment of amebiasis (92, 93.) Manson-Bahr believes that chinifon in combination

with emetine bismuth iodide is especially effective in the very resistant cases (93.) Diodoquin and entero-vioform also deserve therapeutic consideration. Carbarsone, an arsenical compound, is a good supplement or substitute to chinifon (92.)

Gangrene of the skin of the abdominal wall may be caused by the purulent drainage from an amebic hepatic abscess (94.) Amebic dysentery and carcinoma of the terminal bowel may occasionally coexist (95.); hence all granulomatous masses of the colon within the reach of the sigmoidoscope should be studied histologically.

*Giardiasis:* The giardia parasitizes the mucosa of the upper intestinal tract and may invade the common bile duct (92.) The predominant symptoms of giardiasis is diarrhea with or without blood in the stools (96.) Atabrine is an effective lamblicide (96, 97, 98, 92.)

*Deficiency States:* The occurrence of diarrhea in vitamin deficiencies has frequently been observed. However, the exact relationship is still poorly understood; one cannot always be sure of what is cause or effect. Lepore and Golden (99) studied a group of 30 patients with a nutritional deficiency and described a syndrome characterized by malnutrition, a flat oral dextrose tolerance curve and an abnormal small intestine Roentgen-ray pattern. Diarrhea occurred in one-fourth of these patients. Voluntary dietary restrictions and therapeutic diets prescribed by physicians were causative in many patients; most of these patients lived on diets high in carbohydrate and deficient in protein, fat and Vitamin B complex. Vitamin B complex is curative of this disorder. The reviewer has seen a number of patients suffering from diarrhea whose colons appeared normal on sigmoidoscopic and Roentgen-ray examinations; hypochlorhydria was present in some of these patients. A regimen consisting of a balanced bland diet, of Vitamins A, B complex and D, and of glutamic acid hydrochloride (in the presence of hypochlorhydria) produced marked improvement or cures.

The possible relationship of avitaminosis to the development of clinical manifestations of bacillary dysentery has already been alluded to (83.) The status of Vitamin K (lack of) in diarrhea is receiving intensive study.

*Juvenile Diarrhea:* For the sake of special emphasis diarrhea of the juveniles is discussed separately insofar as possible.

An important clinicoepidemic, pathologic and therapeutic study of epidemic diarrhea of the newborn was made by Lyon and Folsom (100.) They investigated an epidemic of diarrhea of the newborn which occurred in the nursery of a general hospital in 1926, 1934, and again in 1938. Suggestive evidence was furnished to prove that this malady is produced by the influenza virus and not by the usual enteric pathogens, including *B. dysenteriae*. Three of the most severely ill infants were benefited by a transfusion of citrated whole blood obtained from a patient recently convalescent from influenza. Normal adult blood given as a control to 3 other sick infants had no therapeutic effect.

The pathogenic significance of the *Bacillus Morgani*, Type I, in enterocolitis of infants was discussed by Neter and Bender (101.) In 3 of their cases, the

necropsy revealed a pseudomembranous enterocolitis, and in another case, catarrhal enterocolitis was present. A mother harboring the Morgani Bacillus, Type I, in the intestine apparently infected her twins who developed enterocolitis (B. Morgani) at the same time. Evidence that newborn infants may acquire intestinal infections from their mothers is furnished by Greenberg, Frant and Shapiro (102) who reported a case of bacillary dysentery, Flexner, in a newborn infant who acquired the disease from its mother after 50 hours of contact.

Root (103) stated that from 500 to 800 babies under 2 years of age die yearly of "diarrheal" disease in North Carolina. It is therefore refreshing to read a report emanating from that state, which deals with the successful treatment of bacillary dysentery in infants (104.) The treatment consists of starvation of fats and proteins for 5 days and the administration of: (1) sulfanilamide; (2) large quantities of fluids (2000 to 4000 cc. of Ringer's solution), and (3) vitamins. Transfusions of blood are given whenever indicated. This form of therapy is enthusiastically endorsed by Jones (105) who had treated at home seventy-odd rural cases of juvenile bacillary dysentery without a mortality.

Nonspecific ulcerative colitis as observed in 23 children was discussed by Elitzak and Widerman (106.) This syndrome in childhood, like that in adults, is characterized by remissions and relapses. The cause is still unknown. At the present there is no specific successful form of therapy. Of this group of patients, 5 cases showed complete healing; improvement occurred in 3, and 6 patients experienced slight or no improvement. Eight of the patients died.

Howell and Knoll (107) discussed amebiasis occurring in infants and children. An incidence of 3.18 per cent of amebiasis was found among 408 children studied as compared to 5.2 per cent encountered among 1.044 adults. A similarly conducted survey for amebiasis in a Chicago orphanage disclosed an incidence of 4.8 per cent. This is in agreement with the general observation that the incidence of amebiasis in institutionalized groups is higher than in other groups. This study also revealed that children apparently have little natural or acquired immunity to amebiasis. Several of the children had symptoms so typical of acute appendicitis that only the early isolation of active amebas prevented operation.

### TUBERCULOSIS

Basunti and Sticotti (108) believe that perianal tuberculous abscesses may develop early or late in the course of tuberculosis without any relation to the progression of the course of the pulmonary lesion and that tubercle bacilli reach the perianal tissues by the hematogenous route. Buie and Redding (109) studied 7 patients with anal tuberculosis. Histologic examination confirmed the diagnosis in 6 of 7 patients. Tuberculosis cutis orificialis was found in 4 cases; tuberculosis verrucosa cutis was observed in another, and a form of hematogenous tuberculosis or sarcoid was encountered in the sixth case. Evidence of inoculation tuberculosis was observed in one instance, and the hematogenous route of dissemination in tuberculosis of the anus was demonstrated histologically in 2 patients. Five patients dated the onset of their

symptoms from the time of the performance of a hemorrhoidectomy which had been performed from 3 months to 9 years previously. In some of these cases healing resulted in anal deformity. These observations suggest that contamination of the anorectal wounds with tubercle bacilli may occur following anorectal operations, such as an elective hemorrhoidectomy, performed upon tuberculous persons.

Pottenger and Pottenger (110) compared the results obtained by dilution-flotation and guinea pig inoculation in the demonstration of *Mycobacterium tuberculosis* in 18 anorectal abscesses. The two laboratory procedures were in 100 per cent agreement in 13 abscesses aspirated by needle, and in only 3 of the 5 abscesses which had ruptured spontaneously with the consequent loss of the purulent material. These results can be explained by the fact that the number of tubercle bacilli increase greatly at the time of caseation and liquefaction. Following the loss of the purulent material by spontaneous rupture or incision, the organisms decrease rapidly. Dilution-flotation with picric acid counterstain offers a definite diagnosis within 2 hours in the abscess stage of anorectal tuberculosis, and appears to be superior to other laboratory diagnostic procedures.

### ACTINOMYCOSIS

Steenrod (111) reported the eighteenth case of anorectal actinomycosis. The portal of entry of the actinomycetes is still undetermined; direct contamination of anorectal wounds may occur by cleansing the anus with contaminated leaves or grass. The diagnosis is made by the finding of the so-called "sulfur granules" in the exudate or within the involved tissues. Recently (112) it has been shown that sulfanilamide is effective in the treatment of actinomycosis.

### VENEREAL DISEASES

*Lymphogranuloma Venereum*: Sulkin and his collaborators (113) substantiated the diagnostic value of lygranum, a new Frei antigen prepared from the infected yolk sac of the developing chick embryo. Yolk sac antigen will replace the antigen prepared from infected mouse brain or from human pus which is extremely difficult to obtain. Lygranum is superior to mouse brain antigen in sensitivity and specificity. A complement fixation test is now in the process of development.

Costello and Cohen (114) believe that with the clinical recognition of the early lesions of lymphogranuloma venereum the incidence of the late serious, debilitating complications would diminish. Proctitis, the forerunner of the anorectal stricture, is considered a possible early manifestation in both sexes. The authors advocated large initial doses of sulfanilamide, 80 grains (5.2 Gm.) daily for 3 days to be followed by a smaller dose, 30 grains (2 Gm.) daily for relatively long periods of time. Sulfathiazole has yielded equally good results. The sulfonamides cure proctitis caused by the venereal virus. These investigators believe that sulfanilamide is the outstanding single form of therapy for this lesion. Other investigators (115) believe that sulfathiazole is superior to sulfanilamide for this lesion. Findlay (116) observed that p-aminobenzoic acid given with sulfanilamide inhibits to a high degree the therapeutic activity of this drug on the virus of lymphogranuloma venereum. Schamberg



(117) studied the serochemical and clinical response of patients with lymphogranuloma venereum to the treatment with sulfanilamide. Reversion of the hyperglobulinemia toward the normal level was observed to parallel clinical improvement. It is suggested that the increase in blood globulin represents a humoral antibody response against the virus of lymphogranuloma venereum, and that its return to normal under sulfanilamide therapy apparently demonstrates an inhibition of antibody formation through the destruction of the venereal virus.

Sulfaguanidine has also been employed successfully for the treatment of inflammatory proctitis caused by lymphogranuloma venereum (118.) This drug had no effect on the fibrotic stricture of the rectum; in these instances, however, sulfaguanidine is indicated as a pre-operative measure.

The general problems of lymphogranuloma venereum were discussed by Howard (119.) Rectal strictures are of 3 varieties. The first group comprises the simple annular strictures with or without perineal or perirectal sinuses. The tubular strictures which may be associated with sinus formation fall into the second group. To the third group belong the hypertrophic, proliferative and polypoid rectal lesions associated with strictures and sinus tracts. The natural history of this infection is toward the formation of fibrous tissue, scarring and stricture. Dilatation of rectal strictures is definitely contraindicated in the presence of associated, draining sinus tracts. Howard advocates systemic therapeutic means that will improve the debilitated condition of the patient in order to accelerate the natural processes of healing. Surgery may be resorted to at a later date. Patterson (120) discussed the surgical treatment of rectal strictures caused by the virus of lymphogranuloma venereum, and proposed a new mucosal-stripping operation. Colp (121) believes that this operation while it is well conceived is nevertheless a palliative procedure and, therefore, prefers a loop-colostomy with perineal resection in order to remove all the diseased lymph nodes as well as the diseased segment of the bowel; the mucosal-stripping operation should be reserved for those cases in which the loop-colostomy and perineal resection cannot be carried out.

*Anorectal Gonorrhea:* Cohn, Steer and Adler (122) investigated the incidence of anorectal gonorrhea in vulvovaginitis of girls by smear, culture and endoscopic examination. The cultural method was found superior to smears in this study. At some time during the course of the vaginal infection about 45 per cent of the children had a positive rectal culture without clinical evidence of proctitis. In 15 per cent of the cases the rectal cultures were positive and the vaginal cultures negative at the same time. Positive cultures were obtained in the diffusely inflamed as well as in the normal appearing rectums. On the other hand, some children with evidence of rectal inflammation had repeated negative cultures. Several children had positive rectal cultures without vaginal reinfection, while in others, the recurrence of the vaginal infection was ascribed to reinfection from the rectum. In untreated patients, spontaneous cures of the rectal infection were noted before or after the subsidence of the vaginal infection. Estrogenic therapy had no effect on the course of rectal gonorrhea. Sulfanilamide, when effective against the genital infection, also cured

the rectal contamination. However, sulfapyridine was curative of the rectal infection in all cases.

*Syphilis:* Greene and Block (123) investigated 6150 patients of a state psychiatric institution in an attempt to determine the relationship of neurosyphilis to disturbances of the anal sphincter tone. Some loss of tone of the anal sphincter muscle was observed in 376 patients (6.1 per cent.) One hundred and thirty-three of these 376 patients (35 per cent) were subsequently found to have neurosyphilis. A patulous anus is regarded of sufficient importance to make proctologic and neurologic studies mandatory. Complete atonia may be an early sign of tabes dorsalis.

## PRURITUS

Hailey (124) reported further observations on 61 additional patients in substantiation of a previously published belief that pruritus ani et vulvae is a symptom of eczema of the anus and vulva. The indirect cause of the eczema is hereditary while the direct or exciting cause may be an external or internal factor, such as drugs, dyes, clothing, diet, heat and anorectal lesions. Emotions are recognized as excitants capable of causing a relapse or of prolonging the episodes of pruritus. Over 80 per cent of Hailey's patients had positive histories of hypersensitive manifestations either in themselves or in members of their families. Eighty-six per cent had eczema in other parts of the body; 29.5 per cent had hay fever, and 13 per cent had asthma. Radiation therapy in combination with allergic management is advocated. The intermarriage of members of families with hypersensitive manifestations is discouraged. Schapiro and Albert (125) investigated 38 patients with anal pruritus from the standpoint of allergy. Only 2 of this group of patients showed eczema elsewhere in the body; Hailey's observations could not be verified. However, a higher incidence of positive cutaneous reactions to allergens, of positive personal and family histories of allergic manifestations, and of eosinophilia in the circulating blood was observed in this group of patients than in the controls. Pruritus ani and hay fever coexisted in about 18 per cent. In 6 patients, elimination of allergens which showed positive intracutaneous reaction resulted in apparent improvement of pruritus ani.

Perianal subcutaneous injection of oxygen for pruritus ani was suggested by Evans (126) who also stated that H. C. Guess continued this investigation and obtained 80 per cent of cures in a group of over 250 cases. Ingels' (127) report on the successful employment of sodium borate in the treatment of epidermophytosis of the anus and other parts of the body is of special interest to the proctologist.

The effectiveness of tattooing with mercury sulfide in intractable anal pruritus is confirmed by Cantor (128) who also discussed the "proper tattoo technic." He regards tattooing as an office procedure and employs infiltration anesthesia using procaine hydrochloride or the long acting oil-soluble anesthetic solutions. It should, however, be pointed out that the use of the long acting oil-soluble anesthetic solutions in tattooing is the equivalent of employing two distinct forms of therapy and of crediting the good results to only one procedure.

The histologic studies of skin tattooed with mercury sulfide for the treatment of intractable localized pru-



ritus have been reported (129.) Immediately after adequate tattooing there is seen massive deposition of mercury sulfide in the upper portion of the corium and some deposit in the epithelium. Later on, the chemical is localized in the corium as clumps of various sizes, which have a slight but definite tendency to reach the deeper portion of the skin. Evidence of irritation or of foreign body giant cell reaction in the skin commonly seen after the introduction of other foreign substances intracutaneously has not been observed following tattooing with mercury sulfide. The quantity and the distribution of the mercury sulfide deposited intracutaneously by tattoo can be correlated with its therapeutic effectiveness.

The occurrence of circumanal and perineal pruritus in the so-called male climacteric age has been reported for the first time (130.) This pruritus was treated successfully with testosterone propionate. Therapeutically, the androgens in the absence of other therapy, were as effective in these patients as the estrogens are in the treatment of genital pruritus of menopause of some women.

### HEMORRHOIDS

*Historic Aspects:* Laufman (131) discussed the history of the theories of the causation and the treatment of hemorrhoids. The fact that hemorrhoids are frequently alluded to in historic writings emphasizes the influence this lesion had exerted upon man throughout the ages. In the prehippocratic period, all infections of the anal region were regarded as hemorrhoids; this erroneous conception is found in some of the writings of the middle ages. In the period of Hippocrates, hemorrhoids were correctly localized to the rectal veins. In the period of Stahl, a belief was current that the hemorrhoidal veins are intended to receive and eliminate waste products. During the poststahlian period, the theories of the constitutional, nervous, mechanical, and infectious causes were formulated and developed; many of these theories are current today. Hippocrates utilized the surgical procedures of ligation, excision and cautery; these procedures form the basis of the modern hemorrhoidectomies. The methods of treating hemorrhoids have been astonishingly similar in principle throughout the history of medicine.

*Injectational Therapy:* The effectiveness of sodium psylliate solution as a sclerosing agent for the injectational treatment of hemorrhoids has been studied by Reuther and Almquist (132.) Bleeding was controlled more effectively and promptly and fewer injections were required with sodium psylliate than with other sclerosing agents. Pain was a conspicuous post-injection local reaction. Two systemic reactions that responded to the injection of epinephrine solution had also occurred. Blond (133) believes that hemorrhoids (as well as other diseases of the anorectum) are due to a "varicose syndrome of the rectum." This syndrome is believed to be brought about by the backflow of the portal blood through the hemorrhoidal vessels into the caval circulation. Hemorrhoidal varices are thus produced and they secondarily, are the cause of other lesions of the anorectum. Venous "compression" therapy which consists of the submucous injection of quinine dihydrochloride, urethane, procaine and tincture of catechu above the level of the hemorrhoids

is advocated. A sterile perivascular inflammatory reaction is produced which compresses the superior hemorrhoidal veins and thus prevents the backflow from the portal circulation to the vena cava. The American proctologist will find many of these ideas unacceptably oldfashioned; they are included in this review only because of their provocative nature and value.

*Operative Treatment:* Calman (134) contributed another paper dealing with the "submucous" technic of hemorrhoidectomy. The main objects of this operative approach are (1) the conservation of mucosa and anal and perianal skin, thus avoiding the formation of post-operative strictures, and (2) the elimination of post-operative pain. Bacon (135) described an improved technic of hemorrhoidectomy which eliminates trauma to the external sphincter muscle; a subcutaneous bed is provided and the wounds of the skin are sutured either with silk or number 35 alloy steel wire. By employing this last simple expedient, the period of convalescence is reduced. "Sphincterismus," the important factor in the production of pain, is eliminated by this special operative technic and by the use of a water soluble long acting anesthetic solution. Of 416 patients submitted to this combined procedure, 51.4 per cent had discomfort but no pain and therefore did not require a narcotic.

In order to prevent post-operative urinary retention, Helfert and Granet (136) adopted Woodruff and TeLinde's suggestion of injecting 30 cc. of 0.5 per cent of an aqueous solution of mercurochrome into the urinary bladder at the conclusion of an anorectal operation. As a result of this maneuver, acute urinary retention occurred in only 0.8 per cent, while in a previous series of similarly operated upon patients in which no intravesical mercurochrome had been employed, the incidence of urinary retention was 57 per cent.

### ANAL INCONTINENCE

The results obtained with the fascia plastic operative procedure for anal incontinence, as originally described by Wreden and modified by Stone, are analyzed by Stone and McLanahan (137.) Thirty patients, operated upon by 6 surgeons, were studied: the results were regarded as excellent in 12; as good in 9; as fair in 5, and as unsatisfactory in only 4 instances. Failure does not prevent repetition of attempts at repair by the same or other surgical procedures.

### FOREIGN BODIES

Foreign bodies may reach the rectum as a result of inadvertent or deliberate swallowing or may be introduced accidentally through the anal orifice, sometimes as a result of sexual perversion. Buda (138) found 5 foreign bodies in a series of 532 cases of anal fistula seen during a 10 year period at The Brooklyn Hospital. Hayes and Burr (139) ingeniously utilized an ordinary tonsil snare for the removal of a glass vase from the rectum. Any loop wire instrument is regarded as a useful instrument for the removal of foreign bodies of the rectum.

### PERFORATION OF RECTUM AND SIGMOID

Perforation of the bowel from a foreign body inserted through the anal canal, as observed in 8 cases by the surgeons of the University of Rochester, is discussed by Pearse (140.) Perforation was caused

by the sigmoidoscope in 4 cases; by an enema tip in 2, and in 1 each by an electrode and a thermometer. Pearse believes that the healthy rectosigmoid can be perforated by a skilled examiner or by a conscious patient without the realization that an injury has occurred.

Instrumental perforation of the colon as a result of diagnostic or therapeutic procedures performed under vision occurs rarely; the danger comes from blind instrumentation by maneuver. Pearse believes that immediate closure yields the best results; delay of 7 hours or more in operative procedure is always fatal. This is in disagreement with the observations of Sallick who believes that perforation of the rectum or sigmoid occurring during sigmoidoscopic examination may, under certain conditions, be treated conservatively. This is especially true in the case of the aged and poor-risk patients and when there has already been a delay of several hours before a diagnosis was made.

### WAR WOUNDS OF COLON

Based on his experience in the World War I, Lockhart-Mummery (141) advocates immediate operation for all war casualties but not to attempt too much at the primary operation. The rule should be "to do as little as possible at the primary operation, and to do that little as quickly as might be." Many examples of unusual injuries of the colon and rectum are described. Gordon-Watson (142) stated that wounds of the colon were invariably complicated by wounds in the small intestine and other viscera. The wounds in the colon were often large and extremely difficult to close. Fecal extravasation, hemorrhage and retroperitoneal infection were the dreaded complications. Wounds of the rectum may be extraperitoneal or intraperitoneal, or both, and are frequently complicated by wounds of the urinary bladder and buttocks. On the other hand, injuries to the buttocks may be complicated by rectal wounds. A transverse colostomy is advocated for the management of severe and complicated wounds of the rectum. In other rectal wounds, division of the sphincter muscle and the employment of an indwelling rectal tube are indicated. Extravasation, hemorrhage and infection caused by anaerobes and streptococci were the major complications. Gordon-Watson compared the surgery of the World War I casualties to those of the present war, and believes that the results will be better now because of (1) the great advances in anesthesia; (2) availability of blood for transfusion, and (3) reduction of infection with the aid of the sulfanilamides.

### CHRONIC CONSTIPATION

Chronic constipation is a symptom due to either (1) organic disease in the colon, especially the anorectum and, occasionally, to systemic disease, such as vitamin deficiency, especially of Vitamin B complex, thyroid deficiency, or (2) to functional factors. Martin (143) stated that there exists considerable confusion in the literature on the subject of colonic function. The colon is under the control of the autonomic nervous system. In the right half of the colon, absorption of fluid from the liquid fecal residue received from the ileum takes place, and the fecal mass is propelled to the left side of the colon by means of mass movements. The forward mass movements are usually stimulated by the gastro-

colic reflex which in turn is initiated by the ingestion of food. When the fecal current reaches the recto-sigmoid, there arises a desire to defecate, and a part of the fecal contents in the descending colon is eliminated. Reverse mass movements carrying the feces back to the descending or transverse colon may occur if the desire to defecate is ignored. The left colon always stores a variable amount of feces, but the normal rectum, contrary to the common belief, is not a reservoir. Rectal dyschesia is a misnomer for megarectum which etiologically resembles megacolon (144.)

Variation in the frequency of bowel movements is normal. However, a change in the intestinal rhythm in a particular patient is of diagnostic import; the presence of a malignant lesion should be suspected. Constipation caused by organic disease responds to the correction or the elimination of the underlying lesion; that caused by anorectal lesions is easily amendable to surgical treatment.

In the management of functional constipation, the patient and not the constipation should be treated. An individualized, sympathetic survey of the patient's personality and psychosomatic reactions should be instituted. Doty (143) believes that depressed individuals may show a slowing of the intestinal motility while a tendency to acceleration may be found in the elated person.

A bland, well balanced, smooth, bulk producing diet should be prescribed. Martin (143) called attention to Olmstead's studies of common vegetables, such as carrots, lettuce and cabbage which contain a cellulose fiber that is hydroscopic thus producing a large, smooth residue. These vegetables belong to the class of granular agar-agar, and are decidedly different from those of the bran (rough) class.

Cathartic drugs and enemas are seldom required except in the management of the elderly or bedridden patient. Travell (143) has stressed the dangers of the cathartic habit particularly well.

Cascara and senna exert a selective action in the colon. The lubricating value of liquid petrolatum has been questioned. Loewe (143) believes that liquid petrolatum acts as an impregnant and not as a lubricant when it is well emulsified with agar so that the emulsion is stable throughout the intestine. Travell (143) emphasized that mineral oil may retain water in an emulsion and thus increase the bulk of the feces. Many investigators agree that liquid petrolatum interferes with the absorption of the fat soluble Vitamins A, D and K (146, 147.) Cattell (143) stated that there is some absorption of mineral oil as indicated by its deposition in the liver following the administration of large doses.

### ENTEROBIASIS

A quick and simple method of trapping the eggs of *Enterobius vermicularis* on the adhesive surface of Scotch cellulose tape was devised by Graham (148.) The adhesive coated transparent cellulose tape meets all the requirements laid down by Hall for a swab to be used in the diagnosis of enterobiasis. Jones and Jacobs (149) studied the survival of infective-stage eggs of *Enterobius vermicularis* under known conditions of temperature and humidity. The great variation in survival under varying conditions and, especially, the importance of temperature and humidity in connection with the time of survival was empha-

sized. Weller and Sorenson (150) examined 505 children in order to determine the frequency of enterobiasis; 97 (19 per cent) of these children were infested with pinworms. In the positive group, the gastro-intestinal symptoms (excepting loss of appetite) as well as vulvitis and night restlessness occurred in the same frequency as in the uninfected children. However, anal pruritus, perianal cutaneous lesions, enuresis and masturbation were a little more common among the positive group. Apparently, a sub-clinical form of enterobiasis is common as judged by the relatively asymptomatic nature of the infection. Further study is necessary to determine why some patients have symptoms and others do not. Cram (151) presented quantitative evidence to show that enterobiasis is frequently a familial infection. Generally, the incidence was lower in the Negro than in the white families. Hillman (152) and Wax and Cooper (153) have studied the incidence of enterobiasis of the appendix. Considerable variation is seen in the clinical picture so that differentiation from acute suppurative appendicitis is impossible. Except for the presence of pinworms within the lumen, which is essential for the diagnosis, there is no pathologic picture characteristic of enterobiasis of the appendix; in fact, there is usually an absence of an inflammatory process in the appendix (152.)

Gentian violet (92) is about 90 per cent efficient in producing cures provided all infected persons in the family or institution are treated concurrently. The four and one-half hour Seal-Ins or one and one-half hour Enseals coating is superior to the ordinary enteric coating. A total of 50 grains of the drug is administered in dosages of 1 grain three times daily with meals for a period of 8 days, which is followed by one week's rest after which 3 grains daily is again given for a period of 8 days. Phenothiazine (a thiazine dye) is also of definite therapeutic value in enterobiasis (154.) The dosage varies from 4 Gm. (1 Gm. daily) for infants aged 1 to 2 years to 9 Gm. (1.5 Gm. daily) for children of 10 and adults.

#### PREGNANCY AND ANORECTAL LESIONS

The management of anorectal lesions occurring during pregnancy was discussed by Mounsey (155.) Palliative treatment is advised for mixed piles occurring after the fifth month of gestation or earlier in the pregnancy which is complicated by hyperemesis gravidarum or impending eclampsia. Prolapsed, strangulated internal piles are best treated surgically without delay. Perianal hematomas (external thrombosed piles) are best treated by excision, as are anal ulcers. For the latter, as a palliative measure, the long acting, oil-soluble anesthetic solutions may be given a trial on occasion. Perianal, perirectal and ischioano-rectal suppurations should be incised and drained at the earliest opportunity. During labor, rectal protrusion should always be replaced to avoid strangulation.

#### MISCELLANEOUS CONSIDERATIONS

*Melanosis Coli:* Melanosis coli was demonstrated histologically by Tanaka (156) in 72 out of a total of 624 necropsies. The pigment cells were found diffusely distributed in all layers of the mucous membrane. In mild cases, the pigment is more superficially distributed while in the severe cases pigmentation is dis-

cernible in the deeper layers. Most of the pigment cells occur in areas characterized by an active flow of lymph; occasionally the pigment is present in the lymphoid follicles. Melanosis is definitely a function of the histiocytes; no pigment is observed in the lymphocytes. The pigment in melanosis is apparently derived from protein and not from blood or fat; the pigment results from pathologic changes in the intestinal contents and from functional disturbances of the intestinal mucosa. The mucosal surface is first deposited by the pigments which are then carried into the deeper layers by the lymphatics and are finally lodged in the reticular tissues.

*Bleeding from Rectum:* Hunt (157) pointed out that gross bleeding from the colon usually receives proper attention, but that progressive secondary anemia caused by a slowly bleeding intestinal lesion is often unrecognized, uninvestigated and untreated. The significance of hemangiomas (157, 158, 49) of the intestinal tract as a source of blood loss has been stressed. Surgical exploration may be required to establish the correct diagnosis of these intestinal lesions (157.)

*Colonic Allergy:* Trescher (159) believes that the present day tendency toward a broad interpretation of the definition of allergy is responsible for the undue emphasis upon the prevalence of food allergy. The importance of applying Cooke's postulates for determining the etiologic significance of an agent in the causation of an allergic disturbance is stressed.

Thomas and Renshaw (160) reported the proctoscopic observations following the application of powdered food allergens to the rectal mucous membrane of 2 patients who suffered from gastro-intestinal allergy and who reacted negatively to the intra-cutaneous tests with similar allergens. Positive mucosal reactions consisting of erythema, edema and vascular engorgement preceded the patients' abdominal distress. In another paper (161), the authors reported their results of 267 individual tests performed in a group of 76 persons. The patients' suspicions of certain offending allergens were confirmed by positive proctoscopic reactions in about 18 per cent of the cases in which the skin tests were negative. In many instances the proctoscopic and the cutaneous tests agreed. That constitutional reactions may follow proctoscopic testing was demonstrated in a patient who developed severe bronchial asthma after the endoscopic applications of offending allergens to the rectal mucosa.

*Colonic Flatus:* Beazell and Ivy (162) studied the quantity of colonic flatus excreted by the "normal" person by collecting the gas in a thick walled rubber balloon by means of a colon tube. Among the 5 ambulatory subjects studied the 24 hour volume varied between 380 and 655 cc. with a mean value of 527 cc. There was no uniform difference between the quantity of gas egested during the day and night, but the composition of the gas was subject to relatively wide individual variation.

*Influence of Alcohol on Colon:* In an interesting study on the motor response of the colon to alcohol, Adler and his collaborators (163) showed that alcohol tends to alter the type of colonic motility of man without greatly influencing the quantity of motility.

*Volvulus:* An unusually interesting case of volvulus

which resulted in gangrene of the sigmoid colon and which was followed by spontaneous anastomosis between the descending colon and rectum was reported by Miller (164.) The patient, a 12 year old Negress, recovered.

**Intussusception:** Skir (165) reported an instructive case of an acute sigmoidorectal intussusception in an infant, which was reduced in the course of recto-sigmoidoscopic examination. Although conclusions are hardly warranted from the experience of a single instance, the record is nevertheless very suggestive. Saline or barium enemas may occasionally also reduce acute intussusception.

**Sulfonamides:** The rectal absorption of sulfanilamide has been confirmed (166, 167.) The prophylactic and therapeutic value of the local application of sulfanilamide to wounds was investigated by Long and Dees (168). Veal and Klepser (169) and others. Veal and Klepser have stated that the local action of sulfanilamide on bacteria depends upon its molecular con-

centration in the wound and that the prolonged use of concentrated sulfanilamide may retard the cellular growth and vascularization of the granulation tissue. The interference with healing of the wound can, however, be overcome by the employment of a sulfanilamide-allantoin ointment instead of the crystalline powder (169.) I have, for some time, been applying sulfathiazole and sulfa-diazine ointment routinely to wounds following anorectal operations with encouraging results. At first an ointment containing 25 per cent of sulfathiazole in cold cream (U.S.P.) was employed. Recently, this has been superseded by an ointment containing 5 per cent of sulfathiazole, 12 per cent of triethanolamine, 10 per cent of glyceryl monostearate, 4 per cent glycerine and 2 per cent acetyl alcohol.

**New Instruments:** The American contribution to the development of proctosigmoidoscopes has been reviewed by Einhorn (170) who also described a new proctosigmoidoscope.

## REFERENCES

1. Turell, R.: Diseases of Colon and Rectum. *Ann. J. Med. Sci.*, 202:282, Aug., 1941.
2. Kennedy, R. L. J.: Polyps of Rectum and Colon in Infants and in Children. *Am. J. Dis. Child.*, 62:481, Sept., 1941.
3. Phillips, R. B.: Polyps of colon and Rectum: Their Association with Cancer. *Mil. Surgeon*, 88:258, March, 1941.
4. Green, W. W.: Polyps of Lower Sigmoid and Rectum. *Ohio State Med. J.*, 37:38, Jan., 1941.
5. Jackman, R. J.: Relationship of Polyps of Colon to Carcinoma. *Proc. Staff Meet., Mayo Clinic*, 16:11, Jan., 2, 1941.
6. Hirschman, L. J.: Diagnostic Pitfalls in Proctology, read before the New York Proctologic Society, New York City, Nov. 28, 1941.
7. Reimann, S. P.: On Some Pathological Aspects of Carcinoma of Rectum. *Rev. Gastro-Enterol.*, 8:24, Jan.-Feb., 1941.
8. Yeomans, F. C., in discussion on Reimann (7.)
9. Borgen, J. A.: Important Newer Concepts Concerning Cancer of Intestines and Their Bearing on Management. *West Virginia M. J.*, 37:433, Oct., 1941.
10. Waldron, G. W.: Progress in Surgery of Large Bowel. *Texas State J. Med.*, 37:13, May, 1941.
11. Hayes, H. T. and Burr, H. B.: Cancer of Rectum, Sigmoid and Anus. *South. Med. J.*, 34:806, Aug., 1941.
12. Rankin, F. W.: Surgical Treatment of Adenomatosis of Colon. *South. Surgeon*, 10:615, Sept., 1941.
13. Borgen, J. A., Cromer, C. D. L. and Dixon, C. F.: Early Carcinoma of Colon II. Relation Between Subclinical Inflammatory Process and Carcinoma. *Arch. Surg.*, 43:192, Aug., 1941.
14. Collier, F. A., Kay, E. B. and McIntyre, R. S.: Regional Lymphatic Metastases of Carcinoma of Colon. *Ann. Surg.*, 114:55, July, 1941.
15. Lawrence, K. B.: Basal Cell Epithelioma of Anus. *Arch. Surg.*, 43:88, July, 1941.
16. Harris, W.: Carcinoma of Anus Treated by Radiation Therapy. *J. Mt. Sinai Hosp.*, 7:405, Jan.-Feb., 1941.
17. Mayo, C. W.: Malignant Lesions of Lower Portion of Sigmoid, Rectosigmoid, Rectum and Anus, with Special Reference to One-Stage Combined Abdominoperineal Resection. *S. Clin. North America*, 21:1129, Aug., 1941.
18. Case, J. T.: Clinical Approach to Roentgen Diagnosis of Carcinoma of Colon. *Illinois Med. J.*, 80:145, Aug., 1941.
19. Gershon-Cohen, J. and Shay, H.: Carcinoma of Colon. *Pennsylvania Med. J.*, 44:462, Jan., 1941.
20. Hartzell, J. B.: Carcinoma of Large Bowel: Problem of Early Diagnosis. *J. Michigan Med. Soc.*, 40:36, Jan., 1941.
21. Buirge, R. E.: Carcinoma of Large Intestine. *Arch. Surg.*, 42:801, May, 1941.
22. McLaughlin, C. W., Jr. and Dilworth, W. M.: Carcinoma of Rectum. *Nebraska Med. J.*, 26:16, Jan., 1941.
23. Singleton, A. O.: Perineal-Abdominal Operation for Cancer of Rectum. *South. Surgeon*, 10:30, Jan., 1941.
24. Buie, L. A., Jackman, R. J. and Vickers, P. M.: Extrarectal Masses Caused by Tumors of Recto-Uterine or Rectovesical Space. *J. A. M. A.*, 117:167, July, 19, 1941.
25. Goligher, J. C.: Operability of Carcinoma of Rectum. *Brit. Med. J.*, 2:4211, Sept. 20, 1941.
26. Johnson, A. S. and Lombard, H. L.: Estimation of Operative Risk in Patients with Cancer. *New England J. Med.*, 224:759, May 1, 1941.
27. Lamson, O. F.: Resection of Carcinoma of Rectosigmoid with End-to-End Anastomosis of Sigmoid to Rectum. *Northwest Med.*, 40:117, April, 1941.
28. Hogeboom, G. W.: Carcinoma of Sigmoid and Advantages of Devine Colostomy. *J. Missouri M. A.*, 38:20, Jan., 1941.
29. Gregg, R. O. and Dixon, C. F.: Operable Malignant Lesions of Colon Producing Obstruction. *S. Clin. North America*, 21:1143, Aug., 1941.
30. Gibbon, J. H., Jr. and Hodge, C. C.: Aseptic, Immediate Anastomosis Following Resection of Colon for Carcinoma. *Ann. Surg.*, 114:635, Oct., 1941.
31. Koster, H.: Method for Preventing or Diminishing Peritonitis from Leakage After Intestinal Resection or Perforation. *Am. J. Surg.*, 53:248, 1941.
32. Ferguson, L. K.: Treatment of Carcinoma of Rectum and Rectosigmoid by Electrocoagulation. *Internat. Clin.*, 1:199, March, 1940.
33. Bowing, H. H. and Dixon, C. F.: Advances in Treatment of Carcinoma of Rectum. *M. Clin. North America*, 25:915, July, 1941.
34. Roberts, F.: X-ray Treatment of Inoperable Carcinoma of Rectum Without Colostomy. *Brit. Med. J.*, 1:357, March 8, 1941.
35. Gregg, R. O. and Dixon, C. F.: Malignant Lesions of Colon and Rectum: Operability and Prognosis. *Proc. Staff Meet., Mayo Clinic*, 16:657, Oct. 15, 1941.
36. Prognosis in Carcinoma of Rectum, Queries and Minor Notes. *J. A. M. A.*, 117:2202, Dec. 20, 1941.
37. Lockwood, J. S.: Sulfonamide Therapy as Aid to Surgery. *S. G. O.*, 72:307, Feb. 15, 1941.
38. Firor, W. M. and Jonas, A. F.: Use of Sulfanilylguanidine in Surgical Patients. *Ann. Surg.*, 114:19, July, 1941.
39. Vneco, R. L., Hny, L. J. and Stevens, B.: Value of Local Implantation of Crystalline Sulfanilamide About Gastro-Intestinal Anastomoses in Dogs. *Surgery*, 9:863, June, 1941.
40. Rosenburr, S. and Wall, N. M.: Treatment of Diffuse Peritonitis by Direct Intraperitoneal Introduction of Sulfanilamide. *S. G. O.*, 72:568, March, 1941.
41. Throckmorton, T. D.: Peritoneal Response to Powdered Sulfonamide Compounds: Experimental Study. *Proc. Staff Meet., Mayo Clinic*, 16:423, July 2, 1941.
42. Firor, W. M. and Poth, E. J.: Intestinal Antisepsis, with Special Reference to Sulfanilylguanidine. *Ann. Surg.*, 114:663, Oct., 1941.
43. Seley, G. P.: Personal communication to the author.
44. Wilcox, F. C., Jr.: Personal communication to the author.
45. Seaman, J. A. and Binnig, C.: Urological Complications of Cancer of Rectum. *J. Urol.*, 46:777, Oct., 1941.
46. Ewert, E. E.: Comparative Analysis of Urological Complications Following Large Bowel Surgery. *J. Urol.*, 46:764, Oct., 1941.
47. Smith, T. E.: Controlling Colostomies. *Texas State J. Med.*, 37:241, July, 1941.
48. Jennings, W. K.: Colostomy and Its Management. *S. Clin. North America*, 21:259, Feb., 1941.
49. Hunt, V. C.: Hemangioma of Large Bowel. *Surgery*, 10:651, Oct., 1941.
50. Barlow, D.: Simple Ulcers of Caecum, Colon and Rectum. *Brit. J. Surg.*, 28:575, April, 1941.
51. Gault, J. T. and Kaplan, P.: Submucous Lipoma of Colon. *Am. J. Surg.*, 53:145, July, 1941.
52. Kantor, J. L.: Personal communication to the author.
53. Patton, C. L. and Patton, R. J.: Endometriosis of Sigmoid as Cause of Acute Intestinal Obstruction. *Am. J. Surg.*, 53:265, Aug., 1941.
54. Colp, R.: Colonic Spasm as Cause of Intestinal Obstruction. *Surgery*, 10:270, Aug., 1941.
55. Winking, A. A.: Acute Diverticulitis of Colon. *Pennsylvania Med. J.*, 44:1318, July, 1941.
56. Evers, C.: Acute Diverticulitis and Sigmoiditis. *Ann. Surg.*, 113:15, Jan., 1941.
57. Babcock, W. W.: Diverticulitis. *Rev. Gastro-Enterol.*, 8:77, March-April, 1941.
58. Lium, R.: Peptic Ulcer and Diarrhea Following Removal of Peyer's Patch Ganglia in Dogs. *Surgery*, 9:538, April, 1941.
59. Poppe, J. K.: Reproduction of Ulcerative Colitis in Dogs. *Arch. Surg.*, 43:551, Oct., 1941.
60. Bercovitz, Z.: Studies in Cellular Exudates of Bowel Discharges. *Ann. Int. Med.*, 14:1323, Feb., 1941.
61. Paulson, M.: Diagnostic Methods in Chronic Ulcerative Colitis. *Am. J. Clin. Path.*, 11:588, July, 1941.
62. Dragstedt, L. R., Dack, G. M. and Kirsner, J. B.: Chronic Ulcerative Colitis. *Ann. Surg.*, 114:653, Oct., 1941.
63. Swartz, J. H. and Jankelson, I. R.: Incidence of Fungi in Stools of Non-Specific Ulcerative Colitis. *Am. J. Dig. Dis.*, 8:211, June, 1941.
64. Elsom, K. A. and Ferguson, L. K.: Appraisal of Medical Versus Surgical Treatment of Idiopathic Ulcerative Colitis. *Am. J. Med. Sci.*, 202:59, July, 1941.
65. Rankin, F. W. and Johnston, C. C.: Chronic Ulcerative Colitis. *South. Med. J.*, 34:464, May, 1941.
66. Garlock, J. H.: Surgical Treatment of Intractable Ulcerative Colitis. *Ann. Surg.*, 113:2, Jan., 1941.
67. Cave, H. W. and Thompson, J. E.: Mortality Factors in Surgical

- Treatment of Ulcerative Colitis. *Ann. Surg.*, 114:46, July, 1941.
68. Lahey, F. H.: Ulcerative Colitis. *New York State J. Med.*, 41: 475, March 1, 1941.
  69. Standard, S.: Ulcerative Colitis with Manifestations of Metabolic and Nutritional Deficiency: Two-Stage Colectomy; read before the New York Surgical Society, New York City, Nov. 26, 1941.
  70. Bancroft, F. W., in discussion on Standard (69.)
  71. Lindahl, W. W. and Borgen, J. A.: Nephrolithiasis Complicating Chronic Ulcerative Colitis After Ileostomy. *J. Urol.*, 46:183, Aug., 1941.
  72. Quinlivan, J. J.: Milk-Borne Bacillary Dysentery. *New York State J. Med.*, 40:1027, July 1, 1940.
  73. Wilson, W. J. and Blair, E. M. McV.: Tellurite-Iron-Rosalic Acid Medium Selective for B. Dysenteriae (Flexner.) *Brit. Med. J.*, 2:501, Oct., 1941.
  74. Ravenel, S. F. and Smith, D. L., Sr.: Chemotherapy of Bacillary Dysentery. *South. Med. J.*, 34:504, May, 1941.
  75. Bell, G. J.: Treatment of Bacillary Dysentery with M. & B. 693. *Lancet*, 241:101, July 26, 1941.
  76. Ching, R. C., Warr, O. S., Jr. and Witherington, J. B.: Treatment of Bacillary Dysentery with Sulfathiazole. *J. Tennessee M. A.*, 34:171, May, 1941.
  77. Taylor, G.: Sulfathiazole Therapy of Infantile Diarrhea. *J. Pediatr.*, 18:469, April, 1941.
  78. Cooper, M. L., Zucker, R. L. and Wagoner, S.: Sulfathiazole for Acute Diarrhea and Dysentery of Infants and Children. *J. A. M. A.*, 117:1520, Nov. 1, 1941.
  79. Marshall, E. K., Jr., Brctton, A. C., Edwards, L. B. and Walker, E.: Sulfanilylguanidine in Treatment of Acute Bacillary Dysentery in Children. *Boll. Johns Hopkins Hosp.*, 68:94, Jan., 1941.
  80. Lyon, G. M.: Chemotherapy in Acute Bacillary Dysentery. *West Virginia Med. J.*, 37:54, Feb., 1941.
  81. Anderson, D. E. W. and Cruickshank, R.: Treatment of Bacillary (Flexner) Dysentery with Sulphanilylguanidine. *Brit. Med. J.*, 2:497, Oct. 11, 1941.
  82. Kilewe, H. and Helmreich, W.: Dysentery Bacteriophages. Abstracted. *J. A. M. A.*, 117:1713, Nov. 15, 1941.
  83. Avitaminotic Dysentery. Editorial. *J. A. M. A.*, 116:2169, May 10, 1941.
  84. Kertesz, Z. I., Walker, M. S. and McCay, C. M.: Effect of Feeding Apple Sauce on Induced Diarrhea in Rats. *Am. J. Dig. Dis.*, 8:124, April, 1941.
  85. Werch, S. C. and Ivy, A. C.: On Fate of Digested Pectin. *Am. J. Dig. Dis.*, 8:101, April, 1941.
  86. Kertesz, Z. I.: Pectic Enzymes. *J. Nutrition*, 20:289, Sept., 1940.
  87. Adler, S. and Foner, A.: Culture of Intestinal Protozoa. *Lancet*, 1:243, Feb. 22, 1941.
  88. Snyder, T. L. and Meloney, H. E.: Excystation of Endamoeba Histolytica in Bacteriologically Sterile Media. *Am. J. Trop. Med.*, 21:63, Jan., 1941.
  89. Rees, C. W., Reardon, L. V., Jacobs, L. and Jones, F.: Problems Encountered in Growth of Endamoeba Histolytica in Cultures Developed by Micro-Isolation. *Am. J. Trop. Med.*, 21:567, July, 1941.
  90. Faust, E. C.: Amebiasis in New Orleans Population as Revealed by Autopsy Examination of Accident Cases. *Am. J. Trop. Med.*, 21:35, Jan., 1941.
  91. Johnson, C. M.: Observations on Natural Infections of Endamoeba Histolytica in Ateles and Rhesus Monkeys. *Am. J. Trop. Med.*, 21:149, Jan., 1941.
  92. Faust, E. C.: Chemotherapy of Intestinal Parasites. *J. A. M. A.*, 117:1331, Oct. 18, 1941.
  93. Minson-Bahr, P.: Amoebic Dysentery and Its Effective Treatment. *Brit. Med. J.*, 2:255, Aug. 23, 1941.
  94. Wyatt, T. E. and Buchholz, R. R.: Amebiasis Cutis. *Ann. Surg.*, 113:140, Jan., 1941.
  95. Landsman, A. A.: Amebic Dysentery as Complication in Diagnosis of Carcinoma of Rectum. *New York State J. Med.*, 41:1181, June 1, 1941.
  96. Nutter, P. B., Rodaniche, E. C. and Palmer, W. L.: Giardia Lambia Infection in Man. *J. A. M. A.*, 116:1631, April 12, 1941.
  97. Calbertson, J. T.: Specific Chemotherapy of Giardia Infections. *J. Lab. and Clin. Med.*, 26:1465, June, 1941.
  98. Hartmao, H. R. and Kyser, F. A.: Giardiasis and Its Treatment: Clinical Study. *J. A. M. A.*, 116:2835, June 28, 1941.
  99. Lepore, M. J. and Golden, R.: Syndrome Due to Deficiency of Vitamin B Complex. *J. A. M. A.*, 117:918, Sept. 13, 1941.
  100. Lyon, G. M. and Folsom, T. G.: Epidemic Diarrhea of Newborn. *Am. J. Dis. Child.*, 61:427, March, 1941.
  101. Neter, E. and Bender, N. C.: Bacillus Morgani, Type 1, in Enterocolitis of Infants. *J. Pediatr.*, 19:53, July, 1941.
  102. Greenberg, M., Frant, S. and Shapiro, R.: Bacillary Dysentery Acquired at Birth. *J. Pediatr.*, 17:363, Sept., 1940.
  103. Root, A. S., in discussion on Keiter (104.)
  104. Keiter, W. E.: Treatment of Bacillary Dysentery in Infants. *North Carolina Med. J.*, 2:479, Sept., 1941.
  105. Jones, C. P., Jr., in discussion on Keiter (104.)
  106. Elitzak, J. and Wilderman, A. H.: Nonspecific Ulcerative Colitis in Childhood. *Am. J. Dis. Child.*, 62:116, July, 1941.
  107. Howell, K. M. and Knoll, E. W.: Amebiasis in Infants and in Children. *Am. J. Dis. Child.*, 61:54, Jan., 1941.
  108. Basanti, V. and Sticotti, S.: Anal Fistula in Tuberculosis. Abstracted. *J. A. M. A.*, 117:898, Sept. 6, 1941.
  109. Buie, L. A. and Redding, M. D.: Anal Tuberculosis. *J. A. M. A.*, 117:1169, Oct. 4, 1941.
  110. Pottenger, J. E. and Pottenger, F. M., Jr.: Demonstration of Mycobacterium Tuberculosis in Anorectal Abscess. *S. G. O.*, 72:936, May, 1941.
  111. Steenrod, E. J.: Anorectal Actinomycosis. *Am. J. Surg.*, 48:567, June, 1940.
  112. Dobson, L.: Holman, E. and Cutting, W.: Sulfanilamide in Therapy of Actinomycosis. *J. A. M. A.*, 116:272, Jan. 25, 1941.
  113. Sulkin, S. E., Fletcher, P. F., Huber, E. T. and Reh, E. P.: Frel Test for Lymphogranuloma Venereum. *J. A. M. A.*, 116:2663, June 14, 1941.
  114. Costello, M. J. and Cohen, J. A.: Lymphogranuloma Venereum. *Arch. Dermatol. and Syph.*, 44:391, Sept., 1941.
  115. Jones, H. P., Rake, G. W. and McKee, C. M.: Chemotherapy of Lymphogranuloma Venereum with Sulfonamide Drugs. *Proc. Soc. Exp. Biol. and Med.*, 48:318, Oct., 1941.
  116. Findlay, G. M.: Action of Sulfanilamide on Virus of Lymphogranuloma Venereum. *Brit. J. Exper. Path.*, 21:356, Dec., 1940.
  117. Schamberg, I. L.: Course of Plasma Protein Changes in Early Lymphopathia Venereum Under Treatment with Sulfanilamide. *Am. J. Med. Sci.*, 201:67, Jan., 1941.
  118. Canizares, O. and Morris, G. E.: Sulfaguanidine in Treatment of Proctitis Due to Lymphogranuloma Venereum. *Arch. Dermatol. and Syph.*, 44:573, Nov., 1941.
  119. Hownd, M. E.: Problems in Lymphogranuloma Venereum. *Internat. Clin.*, 2:157, June, 1941.
  120. Patterson, R. H.: Lymphogranuloma Venereum. *Ann. Surg.*, 114:847, 1941.
  121. Colp, R., in discussion on Patterson (119.)
  122. Cohn, A., Steer, A. and Adler, E. L.: Further Observations on Gonococcal Vulvovaginitis. *Am. J. Syph., Gonorr. and Ven. Dis.*, 25:329, May, 1941.
  123. Greene, B. L. and Block, L. H.: Role of Neurosyphilis in Disturbances of "Anal Sphincter Tone." *Illinois Med. J.*, 79:144, Feb., 1941.
  124. Hailey, H.: Proctitis Ani et Vulvae: Symptom of Eczema. *South. Med. J.*, 34:191, Feb., 1941.
  125. Schapiro, S. and Albert, M. M.: Role of Allergy in Production of Pruritus Ani. *J. Invest. Dermatol.*, 4:219, June, 1941.
  126. Evans, J. H.: Control of Pain and Discomfort by Subcutaneous Injection of Oxygen. *New York State J. Med.*, 41:1927, Oct. 1, 1941.
  127. Inzels, A. E.: Epidermophytosis Treated with Sodium Borate. *California and West. Med.*, 54:120, March, 1941.
  128. Cantor, A. J.: Pruritus Ani. *Am. J. Surg.*, 53:121, July, 1941.
  129. Turell, R.: Tattooing with Mercuric Sulfide for Treatment of Intractable Pruritus Vulvae and Ani: Anatomoclinical Study. *Am. J. Obst. and Gynec.*, 42:290, Aug., 1941.
  130. Turell, R.: Anogenital Pruritus in Male Climacteric: Treatment with Testosterone Propionate. *J. Clin. Endocrin.*, 1:851, Oct., 1941.
  131. Laufman, H.: History of Hemorrhoids. *Am. J. Surg.*, 53:351, Aug., 1941.
  132. Reother, T. F. and Almqvist, C. O.: Injection Treatment of Hemorrhoids: Results with Sodium Psyllate Solution. *Illinois Med. J.*, 75:50, Jan., 1941.
  133. Blond, K.: Hemorrhoids and Their Treatment: Varicose Syndrome of Rectum, translated by E. Stanley Lee, Baltimore, William Wood & Company, 1940.
  134. Calman, A. S.: Submucous Method in Treatment of Anorectal Disease. *Am. J. Surg.*, 53:423, Sept., 1941.
  135. Bncon, H. E.: Anorectal Operative Procedures, with Special Reference to Avoidance of Pain. *J. A. M. A.*, 116:1363, Feb. 1, 1941.
  136. Helfert, I. and Granet, E.: Prevention of Acute Urinary Retention Following Anorectal and Perineal Surgical Procedures. *Am. J. Surg.*, 53:129, July, 1941.
  137. Stone, H. B. and McLanahan, S.: Results with Fascia Plastic Operation for Anal Incontinence. *Ann. Surg.*, 114:73, July, 1941.
  138. Bada, A. M.: General Considerations of Fistula-in-Ano: Role of Foreign Bodies as Causative Factors. *Am. J. Surg.*, 54:384, Nov., 1941.
  139. Hynes, H. T. and Barr, H. B.: Foreign Body in Rectum. *M. Rec. and Ann.*, 35:123, Sept., 1941.
  140. Pearce, H. E.: Instrumental Perforation of Rectosigmoid. *Arch. Surg.*, 42:S50, May, 1941.
  141. Lockhart-Mummery, J. P.: War Wounds of Large Intestine. *Brit. Med. J.*, 1:451, March 16, 1940.
  142. Gordon-Watson, C., in discussion on Lockhart-Mummery (141.)
  143. Conference on Therapy: Management of Constipation. *New York State J. Med.*, 41:1959, Oct. 1, 1941.
  144. Delano, J. P., Ronayne, F. J. and Boland, T. B.: Rectal Dyschezia: Misnomer for Megorectum. *Radiology*, 37:730, Dec., 1941.
  145. Ballou, H. C. and Goldbloom, A.: Serious Injury to Rectum from Improperly Administered Enemas. *Canad. M. A. J.*, 45:345, Oct., 1941.
  146. Morgan, J. W.: Harmful Effects of Mineral Oil (Liquid Petroleum) Purgatives. *J. A. M. A.*, 117:1335, Oct. 18, 1941.
  147. Javert, C. T. and Macri, C.: Prothrombin Concentration and Mineral Oil. *Am. J. Obst. and Gynec.*, 42:409, Sept., 1941.
  148. Graham, C. F.: Device for Diagnosis of Enterobius Infection. *Am. J. Trop. Med.*, 21:159, Jan., 1941.
  149. Jones, M. F. and Jacobs, L.: Studies on Oxyuriasis. *Am. J. Hyg.*, Sect. D, 33:85, May, 1941.
  150. Weller, T. H. and Sorenson, C. W.: Enterobiasis. *New England J. Med.*, 224:143, Jan. 23, 1941.
  151. Cram, E. B.: Studies on Oxyuriasis. *M. Ann.*, District of Columbia, 10:39, Feb., 1941.
  152. Hillman, R. W.: Oxyuriasis of Appendix. *Brooklyn Hosp. J.*, 3:83, April, 1941.
  153. Wax, W. V. and Cooper, N. S.: Oxyuris Vermicularis Appendicitis. *Am. J. Surg.*, 62:89, April, 1941.
  154. Kultunen-Ekbaum, E.: Phenothiazine in Treatment of Enterobiasis. *Canad. Pub. Health J.*, 32:308, June, 1941.
  155. Moansey, J. W.: Management of Anorectal Pathology in Obstetrics. *Northwest Med.*, 40:176, May, 1941.
  156. Tanaka, T.: Melanosis Coli. Abstracted. *J. A. M. A.*, 117:1397, Oct. 18, 1941.
  157. Hunt, V. C.: Surgical Significance of Gastro-Intestinal Bleeding. *Rocky Mountain Med. J.*, 38:196, March, 1941.
  158. Griggs, D. E. and Baker, M. Q.: Hereditary Hemorrhagic Telangiectasia with Gastro-Intestinal Bleeding. *Am. J. Dig. Dis.*, 8:344, Sept., 1941.
  159. Trescher, J. H.: Limitations of Food Allergy. *Med. Clin.*, North America, 25:529, March, 1941.
  160. Thomas, J. W. and Renshaw, R. J. F.: Proctoscopic Observations in Gastro-Intestinal Allergy. *Cleveland Clin. Quart.*, 8:17, Jan., 1941.
  161. Thomas, J. W. and Renshaw, R. J. F.: Gastro-Intestinal Allergy: Proctoscopic Observation. *South. Med. J.*, 34:528, May, 1941.
  162. Beazell, J. M. and Ivy, A. C.: Quantity of Colonic Flatus Ex-



- creted by "Normal" Individual. *Am. J. Dig. Dis.*, 8:128, April, 1941.
163. Adler, H. F., Benzell, J. M., Atkinson, A. J. and Ivy, A. C.: Motor Response of Colon to Alcohol. *Quart. J. Stud. on Alcohol*, 1:638, March, 1941.
164. Miller, E. M.: Gangrene of Sigmoid Flexure of Colon Due to Volvulus. *Arch. Surg.*, 41:103, Aug., 1940.
165. Skir, I.: Acute Sigmoidorectal Intussusception. *Rev. Gastro-Enterol.*, 8:232, May-June, 1941.
166. Strauss, E., Lowell, F. C., Taylor, F. H. L. and Finland, M.: Observations on Absorption, Excretion and Distribution of Sul-

- fanilamide, Sulfapyridine, Sulfathiazole and Sulfamethylthiazole. *Ann. Int. Med.*, 14:1360, Feb., 1941.
167. Wood, E. H.: Sulfanilamide Per Rectum. *Canad. M. A. J.*, 44:592, June, 1941.
168. Long, L. W. and Dees, J. G.: Local Use of Sulfanilamide. *Surgery*, 9:578, June, 1941.
169. Veal, J. R. and Klepser, R. G.: Local Sulfanilamide Therapy in Surgical Infections. *Surgery*, 10:947, Dec., 1941.
170. Einhorn, M.: New Proctosigmoidoscope with Review of American Contribution to Development of These Instruments. *Rev. Gastro-Enterol.*, 8:218, May-June, 1941.

## Gastric Similarities and Differences Between Tropical Sprue and Pernicious Anemia\*

By

A. RODRIGUEZ OLLEROS

SAN JUAN, PUERTO RICO

**I**NVESTIGATION in the differential diagnosis between tropical sprue and pernicious anemia is of great practical value, in addition to its importance in the realm of research.

In the light of our present knowledge of the syndromes of both illnesses, it would be perfectly logical to advise a sprue patient to seek benefit from change of climate, advice which would be useless were he suffering from pernicious anemia.

According to Azmy and Zanaty (1), Addisonian anemia is very rare in those races indigenous to the tropics; however, we must take into consideration the fact that in the present day the facility of transportation of groups of people is such that no one country can be said to be absolutely immune from any disease, even if the social and climatic conditions are unfavorable for its development.

One thing is certain—it is impossible in some cases to establish an exact differential diagnosis between tropical sprue and pernicious anemia. It is then that one must turn to laboratory procedures, although they have, up to the present, not been of outstanding practical value.

From a review of the literature published during the last two years on this subject, one may consider of value these words of Rhoads and Miller (2):

"Thus the only difference between certain cases of sprue and of pernicious anemia was that a substance rich in the water-soluble vitamin was therapeutically effective per se, at least in certain cases of sprue, whereas it was effective in pernicious anemia only after it had been incubated with normal gastric juice."

Davison (3) and Wintrobe (4) arrived at this same conclusion, although they pointed out the existence of exceptional cases of pernicious anemia having been cured by the administration of large quantities of autolyzed yeast *per os*.

The fundamental differential gastrologic fact of these two anemias, a physiopathologic fact, in Castle's concept, is founded on the absence in effective quantity of the intrinsic principle in the gastric juice of those patients suffering from pernicious anemia. But although the demonstration of this intrinsic principle is

possible, we have not yet arrived at any practical method of achieving it.

Recently, Gessler (5) and his collaborators have observed in normal gastric juice a proteolytic enzyme capable of hydrolyzing caseine, liberating the proteases. It is an enzyme which acts in an alkaline medium—a quality which distinguishes it from pepsin; on the other hand it is differentiated from trypsin and erepsin because it does not liberate nitrogen in large quantities. They think that this ferment is identical with Castle's intrinsic factor, and they have found that it does not exist in the gastric juice of patients suffering from pernicious anemia. Further investigation of this protease of Gessler's is necessary before one can come to a definite conclusion.

Of those other usual tests which may be made in the stomach, the most frequent is that of the curve of hydrochloric acid secretion which alone may differentiate a large number of tropical sprue cases from those of pernicious anemia. It is generally accepted that histamine resistant achlorhydria is a never failing concurrent characteristic of pernicious anemia. Only a few authors, like Hurst (6), admit the existence of exceptional cases of pernicious anemia with free hydrochloric acid.

In cases of tropical sprue only about 30 per cent approximately, present histamine resistant achylia. These cases show much similarity with those of pernicious anemia, and can only be differentiated by the differences pointed out by Rodríguez Ollerós and Hernández Morales (7) in the time of elimination of neutral red through the gastric mucosa in the two conditions.

On this basis we shall discuss in their order the bacteriological aspects, the gastroscopic and chromoscopic, with neutral red, in patients with tropical sprue as observed in Puerto Rico, and compare the results with those obtained by different authors who have carried out similar investigations on cases of pernicious anemia of non-tropical countries.

### BACTERIOLOGY

Normally the gastric content is sterile, chiefly on account of the impossibility of bacterial development in media with as low a pH as that which obtains in gastric juice, because of its hydrochloric acid content.

In cases of pernicious anemia the stomach is nearly always invaded by the flora of the coli group (Katsch

\*Read before the Annual Medical Convention of San Juan, Puerto Rico, December, 1941.  
Submitted January 25, 1942.



(8) and Dick (9)) to such a degree that this invasion is considered as one of the characteristics of the so-called pernicious achylia, while in those designated as functional achylia a bacterial growth of that type is not found in the stomach, (Henning and Norpoth (10)) probably because there is no gastroscopic evidence of atrophy. This fact alone draws attention to the possibility of the existence of other factors besides the hydrochloric acid content which may contribute to the sterility of the gastric juice.

In 25 cases of tropical sprue studied in the School of Tropical Medicine, the second gastric sample obtained during fasting was examined in the Department of Bacteriology of the School\* with the following results:

|   |    |
|---|----|
| Total number of cases .....                   | 25 |
| With gram positive and gram negative flora... | 14 |
| With gram negative flora only .....           | 8  |
| With gram positive flora only .....           | 1  |
| Sterile .....                                 | 2  |

Of these 25 cases, only two showed histamine resistant achlorhydria, which leads one to believe that other factors, apart from achlorhydria, are responsible for the loss of sterility in the gastric juice of these patients.

Lloyd Arnold (11) has effectively demonstrated the disturbance of those factors which ensure sterility of the gastric juice in tropical regions. This author has operated on 25 dogs, fixing underneath the skin in such a manner that sterile punctures might be made, loops from different levels of the intestines. These dogs were placed in special compartments of the kind used for the cultivation of tropical plants, at 90° F. and 86 per cent to 90 per cent humidity, and it was found out that the upper parts of the intestinal tract lose the power of self-sterilization and permit the invasion by the flora common to the lower levels.

One of the factors which aids the hydrochloric acid in its function of sterilizing the stomach is the very small quantity of sulphocyanate which, independent of that secreted by saliva, is found in the gastric juice. In gastric juice taken from fasting patients there is contained sulphocyanate (CNS) in amounts which vary between 1.3 and 2.32 milligrams per cent. Brinck (12) has found high values in peptic ulcer cases and low, in cases of tuberculosis and pernicious anemia. To date no investigation has been made as to the amount of sulphocyanate contained in the gastric juice of sprue patients, and perhaps the results of such a study might in part explain why the stomach in sprue is so easily colonized by the flora of the large intestine, even though in the great majority of cases free hydrochloric acid is present in the gastric juice.

### GASTROSCOPY

Comparing the gastroscopic descriptions of pernicious anemia given by Henning (13), Jones, Benedict and Hampton (14), Moutier (15), Gutzeit and Teitge (16), and Schindler and Serby (17), with those made by ourselves (18) in cases of tropical sprue, there may be noted at first glance certain analogies referring to the type of lesion of the gastric mucosa and, at the same time certain differences in the severity of the lesions.

\*In connection with this investigation I wish to pay tribute to the memory of Dr. Cecilia Benitez, who at the time of her death, was working with outstanding effect in the Dept. of Bacteriology, the School of Tropical Medicine.

In pernicious anemia it is usual to meet with an atrophic gastritis which, according to some authors, is predominant in some areas and which, according to others, is generalized. These lesions improve with liver therapy to the point where (in many cases), after a course of treatment the atrophic gastritis, as observed through the gastroscope, undergoes complete cure.

We have carried out gastroscopic investigations in three groups of tropical sprue patients. In the first group, all the cases except one, presented the syndrome of tropical sprue with atrophic gastritis, sometimes localized, but in the majority of cases, generalized. In no case, however, was the gastritis as severe as that we had previously observed by means of the rigid gastroscope in cases of pernicious anemia in temperate climates (19.)

In the group evidencing the incomplete syndrome of tropical sprue we found, also in the majority of cases atrophic gastritis, but of even lesser intensity than in the preceding group.

Finally, in the group with latent sprue, the symptoms of which had been checked by nearly all the patients by means of liver therapy, the predominance of the gastroscopic characteristics had disappeared from the atrophic gastritis. In these cases there persisted an atrophic gastritis but rarely. In some, the mucosa was normal; in others there was superficial gastritis; and in a few, the picture was that of hyper-trophic gastritis.

We cannot accept without reserve the exact correlation of the gastroscopic with the histologic picture, especially in the cases of moderate gastroscopic alterations (Swalm and Morrison (20).) For this reason it appears to us that the criterion expressed by Miller (21) is worthy of being followed, and that is to describe, instead of classifying, the gastroscopic observations. If we follow that criterion, the gastroscopic description of the stomach in the syndrome of tropical sprue coincides with that of pernicious anemia, but with signs less accentuated. Also, in both illnesses, there is coincidence in their improvement under liver therapy.

But as this improvement, as shown by gastroscopy, which may be produced in cases of pernicious anemia by liver therapy according to what Carey (22) has observed, is never accompanied by histologic restoration, we may as well ask if the same thing occurs in cases of sprue which gastroscopically show improvement as a result of liver therapy. On the other hand the question should also be propounded as to whether the atrophic aspect really corresponds, as happens in pernicious anemia, with real histologic atrophy.

If we remember that 90 per cent of our cases of complete sprue were suffering from gastric atrophy, gastroscopically, and that only 33 per cent had histamine-resistant achylia, we must conclude that in some of the cases the gastric atrophy seen through the gastroscope is not accompanied by functional atrophy and, therefore, histologic atrophy does not exist in these cases, while it is always present in pernicious anemia.

One must not forget that the gastroscopic appearance and the apparent improvement by liver therapy may be owing more to true and profound histologic changes of the gastric mucosa, to variations in the

blood supply with its consequent effect on the thickness of the mucosa. But there is a group of sprue patients with gastroscopic signs of atrophy and complete gastric achylia, as in pernicious anemia, in whom the study of the secretion of neutral red through the gastric mucosa may be of value in differentiating between the two conditions.

### CHROMOSCOPY

The function of gastric excretion of neutral red administered by the parenteral route is the last activity that the stomach loses in the course of mucosal atrophy. Henning and Jurgens (23) maintain, founding their belief on the gastroscopic study of 161 patients tested with neutral red, that in severe atrophic gastritis, considered typical of pernicious anemia, the neutral red is not eliminated; whereas, in cases of histamine-resistant achlorhydria without serious atrophic lesions, the neutral red is eliminated by the gastric mucosa.

Katsch and Kalk (24) have come to similar conclusions, presenting as an example a case of gastritis following an attempt to commit suicide by swallowing acid, in which they observed that once the first period of "exhaustion" or refractoriness was passed, during which the mucosa gave no sign of any activity, regeneration of the mucosa began with elimination or secretion of neutral red as the first sign; next came an increase in the secretion of total chlorides; next came the secretion of free HCl, but only under histamine stimulation, and, finally, the hydrochloric acid appeared after less potent stimuli such as caffeine, given by mouth. That is to say, in an inverse sense, in progressive atrophy the successive losses are: (a) spontaneous secretion of free hydrochloric acid; (b) the loss of secretion of hydrochloric acid, even when stimulated with histamine; (c) secretion of total chlorides and (d) in the last instance, the excretion of neutral red.

Many other investigators have also noted that it is characteristic of pernicious anemia to show a histamine-resistant achylia, and the total absence of excretion by the gastric mucosa of the neutral red which has been injected intramuscularly or intravenously (Davison, Willcox and Haagensohn (25), Winkelstein and Marcus (26), Streicher (27), Held (28) and Morrison (29).)

In a former work made in collaboration with Hernández Morales, we recorded the result obtained from the test of gastric elimination of neutral red in 27 patients suffering from tropical sprue which had been seen in the Dispensary of the School of Tropical Medicine. We now add 22 additional cases of tropical sprue seen in the Clínica Pereira Leal. In all these cases the neutral red test was performed in the following manner:

After a fast of 12 hours, we made a fractional examination of the gastric secretion in each patient, using as stimulant a solution of caffeine (0.2 grams of pure caffeine in 300 cc. of water), colored with two drops of solution of methylene

blue. When this had been evacuated from the stomach, we injected intramuscularly into a buttock 5 cc. of 1% solution of neutral red; in those cases that had shown no evidence of secretion of free hydrochloric acid, we administered simultaneously, a subcutaneous injection of histamine. From the moment of the injection of neutral red, we extracted the gastric contents every 5 minutes until a red coloration appeared. We took that as the time at which the elimination of the injected neutral red began.

TABLE I

Mean time of the beginning of elimination of neutral red in tropical sprue

| Hyperacidity  | Normal    | Hypoacidity | Anacidity |
|---|-----------|-------------|-----------|
| 13.7 min.   | 12.4 min. | 14.4 min.   | 24.2 min. |
| Comparison with normal individuals living in the tropics (32 cases) |           |             |           |
| Hyperacidity  | Normal    | Hypoacidity |           |
| 16.6 min.   | 14.2 min. | 24 min.     |           |

It should be carefully noted that in the anacid group made up of 14 cases, of which 6 had histamine-resistant achylia, all of them were able to eliminate neutral red from the gastric mucosa.

On the other hand, in another two cases with histamine-resistant achylia and gastric atrophy, one of which had the clinical and neurological symptoms characteristic of pernicious anemia, while the other was typical of pellagra, neutral red was not eliminated.

If we correlate the results of our gastroscopic studies of tropical sprue with those obtained in the elimination of neutral red, one must come to the conclusion that in this syndrome the stomach does not reach the grade of atrophy which is the constant component of the picture of pernicious anemia. The difference is easily demonstrable and becomes, therefore, of practical importance. The test of the elimination of neutral red from the stomach, performed as described, has been positive in all our cases of tropical sprue, even in those in which there were clinical and laboratory findings suggestive of pernicious anemia.

### CONCLUSIONS

1. In the great majority of cases of tropical sprue the stomach is invaded by the gram-negative flora of the large intestine, as occurs in pernicious anemia.
2. The mucosal atrophy observed in the gastroscopic examination of individuals suffering from sprue is less marked than that obtaining in cases of the pernicious anemias of temperate climates.
3. Cases of tropical sprue eliminate neutral red by the gastric mucosa, even when there exists a histamine-resistant achylia.
4. We believe that this test may be useful in the differential diagnosis between the two syndromes.

### REFERENCES

1. Pasha, S. Azmy and Zanaty, A. F.: *Lancet*, 11:1359-1362, 1939.
2. Rhoads and Miller: *J. A. M. A.*, CIII:387-391, 1934.
3. Davison, L. S. P.: *Cambridge Med. J.*, LXIV:474-484, 1939.
4. Wintrobe, M. M.: *Am. J. Med. Sci.*, CXCIV:286-310, 1939.
5. Gessler, C. J., Dexter, Adams and Taylor: *J. Clin. Invest.*, XIX: 225-231, 1940.
6. Hurst, A. F.: *British Med. J.*, 11:565, 1934.
7. Ollerós, A. Rodríguez and Morales, F. Hernández: *Am. J. Dig. Dis.*, VII:183-184, 1940.
8. Katsch, G.: *Handbuch Inn. Med.*, J. Springer, Berlin, III:405, 1938.
9. Dick, F. G.: *Am. J. Dig. Dis.*, VIII:255-260, 1941.
10. Henning, N. and Norpoth, K.: *Klin. Woch.*, 11:159-161, 1932.
11. Lloyd, Arnold: *J. Hyp.*, XXIX:82-116, 1929-30.

12. Brinck, J.: *Ztschr. f. Klin. Med.*, CXXIII:350-389, 1933.
13. Henning, N.: *Die Entzündung des Magens*, Leipzig, Birth, 1934.
14. Jones, C. M., Benedict, E. B. and Hampton, A. O.: *Am. J. Med. Sci.*, CXC:596-610, 1935.
15. Moutier, F.: *Traité de Gastrosomie*, Paris, Masson, 1935.
16. Gutzeit, K. and Teitge, H.: *Die Gastroskopie*, Berlin, 1937.
17. Schindler, R. and Serby, A. M.: *Arch. Int. Med.*, LXIII:334-356, 1939.
18. Ollerios, A. Rodriguez: *The P. R. J. of Pub. Health and Trop. Med.*, XIII:503-521, 1938.
19. Ollerios, A. Rodriguez and Viesca, de la: *Act. II Cong. Español Pat. Digest.*, Barcelona, 469-472, 1933.
20. Swalm, W. A. and Morrison, L. M.: *Am. J. Dig. Dis.*, VIII:391-398, 1941.
21. Miller, G.: *International Clinic*, 1:173-178, 1940.
22. Carey, J. B.: *Minnesota Med.*, XXIII:311-313, 1940.
23. Henning N. and Jürgens. *München. med. Wchnschr.*, LXXVII: 1961-1963, 1930.
24. Katsch, G. and Kalk, H.: *Klin. Wchnschr.*, XXV:1119-1123, 1926.
25. Davison, P. B., Wilcox, E. and Haangenson, C. D.: *J. A. M. A.*, LXXXV:794-799, 1925.
26. Winkelstein, A. and Marcus, J. M.: *J. A. M. A.*, LXXXV:1397-1398, 1925.
27. Streicher, M. H.: *J. A. M. A.*, XCV:326-327, 1930.
28. Held, J.: *Arch. d. mal. de l'app. digestif.*, XXIII:827-858, 1933.
29. Morrison, S.: *International Clinic*, 1:119-143, 1938.

## Studies in Human Biliary Physiology

### VI. Composition of Continuously Collected Fractions of Liver Bile on Starvation and after High Carbohydrate Feeding

By

MENDEL JACOBI, M.D., BENJAMIN KOGUT, M.D., I. CHARLES ZUCKERMAN, M.D., LESTER WEIL, M.A.  
and

BERNARD KLEIN, M.A.  
BROOKLYN, NEW YORK

IN preceding papers (1, 2) we discussed the rate and quantity of bile secreted daily by the liver under controlled conditions in the fasting state and under the influence of various food factors. We have been unable to find in the literature any record of continuous fractional analyses of human bile for protracted periods in which the factor of the gall bladder could be eliminated. There are, in fact, few recorded observations on the chemical analysis of human bile in fractional daily specimens (3, 4) and these are limited to ash, solids, and physical constants (3) or cholesterol (4.) The large number of detailed quantitative chemical studies on human bile were performed, in the main, on gall bladder or bile-duct fistula bile, collected without attempting any demonstrable conditions of control, or on bile collected at operation or autopsy and frequently pooled. It is due to such methods of obtaining material for analysis that there are recorded widely divergent figures in the voluminous literature on the subject. This paper will present the results of simultaneous quantitative studies of some of the important constituents of pure hepatic bile, not influenced by the presence of stasis, infection, or a gall bladder, and collected, under controlled conditions, for continuous daily periods.

**Procedure.** With the patient in bed, food was gradually restricted for four days until, on the day before the test day and again on the day on which specimens for analysis were collected, no food at all was consumed. Approximately 800 cc. of water was imbibed by the patient on these latter two days. On the test day samples of bile were collected through her external biliary fistula—her gall bladder had long before been removed and the resulting fistula was totally external, as described in a previous paper (1)—these samples being taken at various times of the day, the interval between collections corresponding to the usual meal intervals, and during the night. After two weeks' rest, this procedure was repeated and

specimens collected for analysis, and, in identical manner was this process repeated twice again, so that, in all, there were available for analysis four separate sets of specimens collected at two-week intervals over a period of two months. All specimens were individually analyzed for urea (5), chlorides (6), total base (7), sodium after ashing of the bile and re-

TABLE I  
*Chemical composition of pure hepatic fistula bile, 24 hour collection. Patient on complete starvation*

| Determined Element        | Value              | Accuracy of Method |
|---------------------------|--------------------|--------------------|
| pH                        | 7.3                |                    |
| Specific gravity          | 1.010 to 1.002     |                    |
| Water                     | 97.41%             |                    |
| Total solids              | 2.59%              | 0.1%               |
| Chlorides                 | 106.0 meq./L       | 0.5%               |
| Carbonate                 | 24.3 meq./L        | 1.0%               |
| Phosphorus (as phosphate) | 5.7 x 3 meq./L     | 3.0%               |
| Total base                | 176.0 meq./L       | 5.0%               |
| Sodium                    | 169.0 meq./L       | 4.0%               |
| Potassium                 | 8.8 meq./L         | 2.0%               |
| Cholesterol               | 158.4 mgm./100 cc. | 3.0%               |
| Fatty acids               | 132.4 mgm./100 cc. | 2.0%               |
| Urea                      | 16.0 mgm./100 cc.  | 1.0%               |

For references to methods of analysis used, see text.

moval of phosphates (8), potassium (9), phosphorus (10), inorganic sulphate (11), cholesterol (12), fatty acid (13), and bicarbonate (14.) The mean values of all the samples for a single 24 hour period are presented in Table I; the values did not vary significantly for the four test periods.

In passing, it may be noted that the quantities of inorganic sulphate present varied from zero to 50

From the departments of pathology and surgery, Beth-el Hospital, Brooklyn, N. Y.

Presented before the Brooklyn Society of Internal Medicine, June, 1941.

Submitted February 10, 1942.

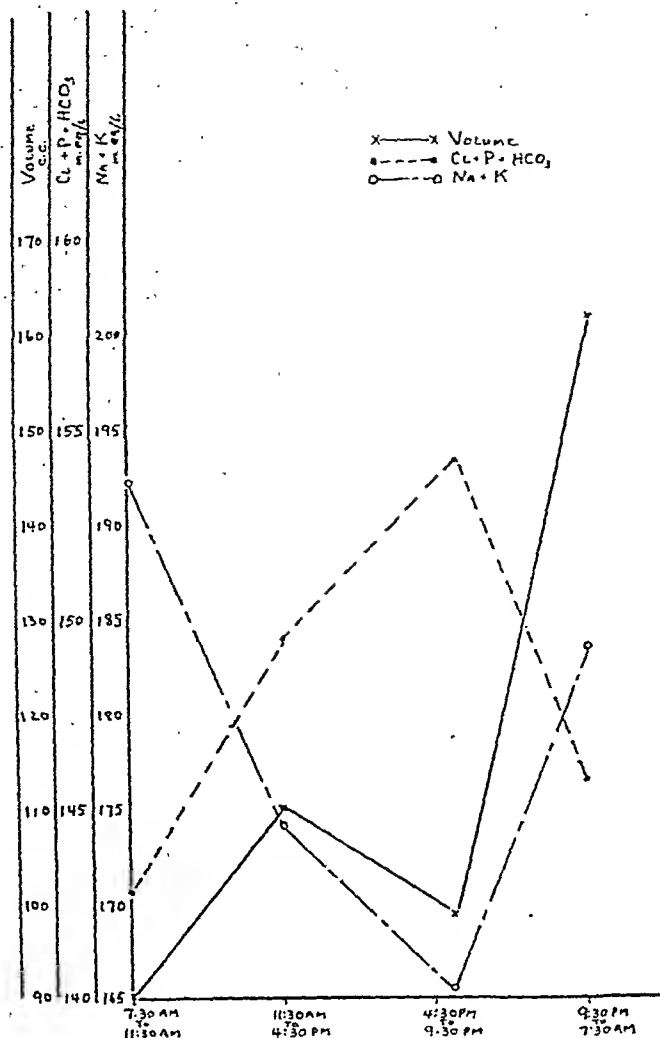


Fig. 1. Relation of anions, cations, and volume of bile excreted. Patient on total starvation.

mgm. per cent, but, with the amount of bile available for analysis at any one time, the values could not be determined with sufficient accuracy to be included in

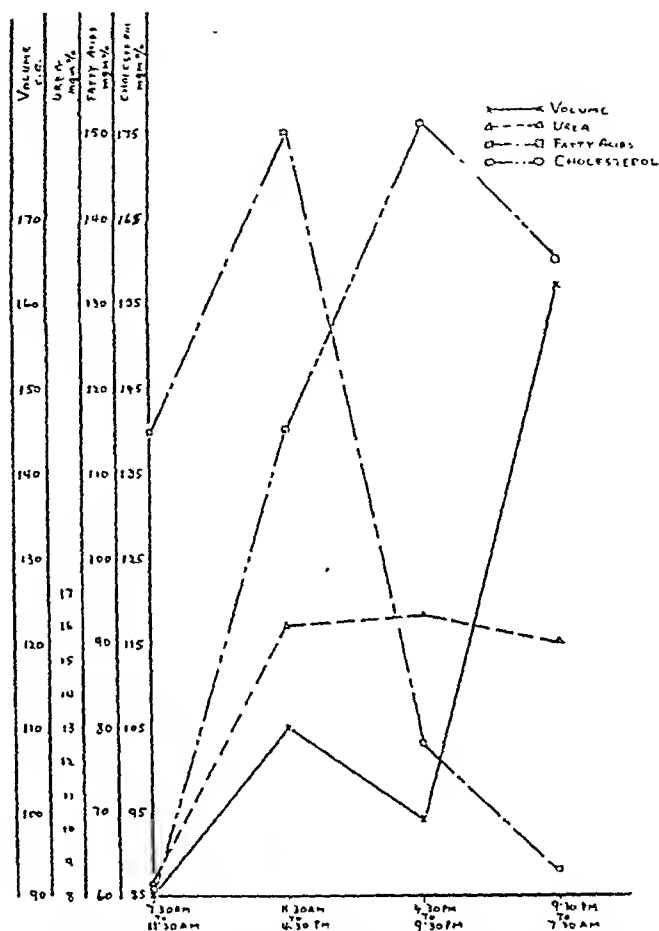


Fig. 2. Biliary urea, fatty acids, cholesterol and total volume for 24 hour period, patient on total starvation.

TABLE II

Composition of pure hepatic fistula bile, Individual samples for 24 hour period

| Composition of Human Fistula Bile<br>Patient on Total Starvation |               |                 |               |                              |                        |                |               |                       |                      |                |
|--|---------------|-----------------|---------------|------------------------------|------------------------|----------------|---------------|-----------------------|----------------------|----------------|
| Period   | Vol.<br>(cc.) | Cl.<br>(meq./l) | P<br>(meq./l) | HCO <sub>3</sub><br>(meq./l) | Total Base<br>(meq./l) | Na<br>(meq./l) | K<br>(meq./l) | Cholesterol<br>mgm. % | Fatty Acid<br>mgm. % | Urea<br>mgm. % |
| 7:30 A.M.  |               |                 |               |                              |                        |                |               |                       |                      |                |
| 11:30 A.M.   | 90            | 99.2            | 18.58         | 25.1                         | 180                    | 183            | 9.1           | 85.8                  | 115                  | 8.2            |
| 11:30 A.M.   |               |                 |               |                              |                        |                |               |                       |                      |                |
| 4:30 P.M.  | 110           | 111.0           | 15.9          | 22.6                         | 178                    | 165            | 9.2           | 140                   | 150                  | 16.0           |
| 4:30 P.M.  |               |                 |               |                              |                        |                |               |                       |                      |                |
| 9:30 P.M.  | 99            | 111.6           | 18.0          | 24.6                         | 163                    | 157            | 8.2           | 176                   | 78                   | 16.2           |
| 9:30 P.M.  |               |                 |               |                              |                        |                |               |                       |                      |                |
| 7:30 A.M.  | 162           | 103.3           | 17.4          | 25.2                         | 182                    | 175            | 8.6           | 160                   | 63                   | 15.5           |
| Patient fed 400 grams glucose                                    |               |                 |               |                              |                        |                |               |                       |                      |                |
| 7:30 A.M.  |               |                 |               |                              |                        |                |               |                       |                      |                |
| 11:30 A.M.   | 86            | 104.5           | 17.4          | 27.5                         | 184                    | 180.5          | 8.1           | 118.2                 | 33                   | 13.3           |
| 11:30 A.M.   |               |                 |               |                              |                        |                |               |                       |                      |                |
| 4:30 P.M.  | 107           | 107.7           | 17.7          | 30.7                         | 162                    | 165.1          | 7.3           | 97.2                  | 94.9                 | 11.7           |
| 4:30 P.M.  |               |                 |               |                              |                        |                |               |                       |                      |                |
| 9:30 P.M.  | 96            | 104.2           | 17.4          | 23.0                         | 170                    | 156.3          | 11.6          | 134.0                 | 88.4                 | 16.4           |
| 9:30 P.M.  |               |                 |               |                              |                        |                |               |                       |                      |                |
| 7:30 A.M.  | 161           | 104.2           | 16.2          | 25.3                         | 177                    | 171.1          | 8.7           | 100.0                 | 54.6                 | 17.2           |

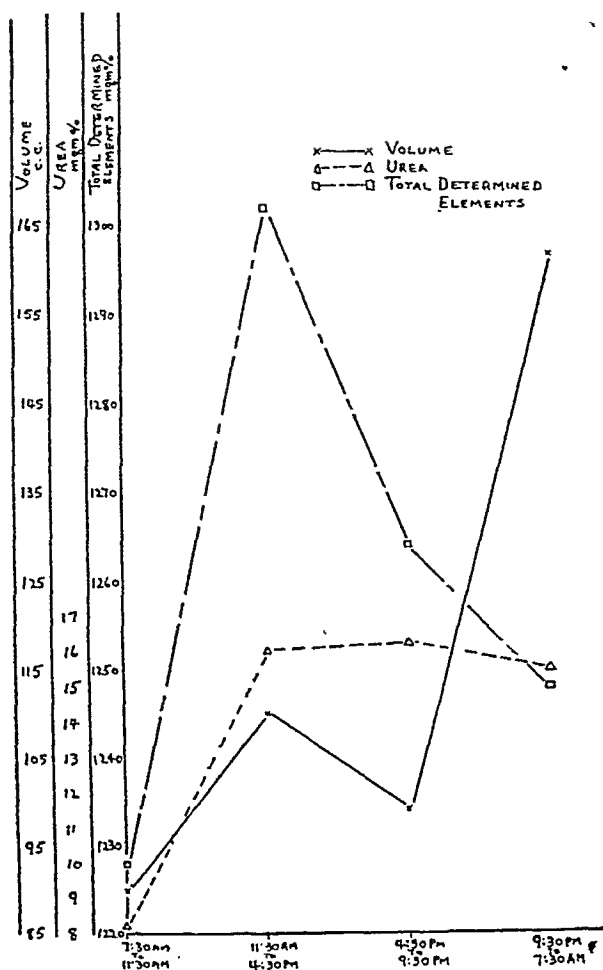


Fig. 3. Relation of all determined biliary elements (see Table II), bile volume and urea for 24 hour period, patient on total starvation.

our results or their discussion. Similarly, phosphatides were present in too small an amount for quantitative determination by methods available to us for use on the fractionally-collected specimens. Cholesterol ester and Fehling-reducing substance was invariably absent in all specimens. The fatty acid figures in all the tables in this paper include free fatty acids and fatty acids from neutral fats and phosphatides, but do not include those possibly derived from soaps.

Table II presents the quantitative values of the various measurable constituents studied over a typical test day in the fractional bile specimens.

At first glance, these values suggest no definite pattern or relationship. When, however, the arithmetically added values of related ions were plotted against those of opposite sign, or when physiologically similar substances or those possibly chemically interrelated were similarly arithmetically plotted against each other and against the volume, suggestive correlations appeared regularly in each of the four test day studies. For the values in Table II, these correlations are graphically represented in Figs. 1, 2 and 3.

From these graphs the following relationships are suggested:

1. Anions and urea vary directly with the total

volume of the excreted bile with a moderate lag on the part of the former.

2. Anions and cations vary inversely with each other. The product of the two is relatively constant.

3. Cholesterol and fatty acids are parallel in concentration in all specimens. The curve of their concentration is roughly similar to that of the arithmetic total of all the constituents determined.

4. Similarly, the sum of all the constituents determined parallels the volume curve for all parts of the day, but the concentration of the biliary constituents decreases during the sleeping hours, as the volume and the amount of water in the bile rises. There is, however, a closer similarity between the volume curve and the sum of all the bile constituents determined in these experiments than between the volume curve and any of the individual constituents.

5. The urea values vary roughly in inverse manner with the sum of all other constituents, and these reach their respective maximal and minimal values at about the same time. Urea was the only biliary constituent determined in these experiments that continued to maintain a high night concentration.

It will be noted that no quantitative determinations of bile salts or acids, or bile pigments or mucin were performed. This was due to the fact that no sufficiently

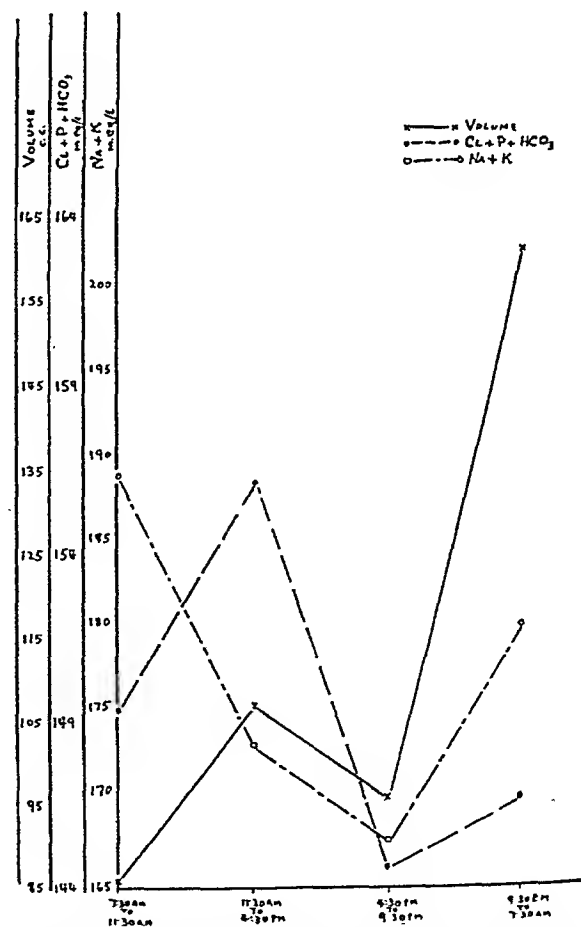


Fig. 4. Biliary anions, cations, and volume for 24 hour period, patient fed 400 grams of glucose. Note similarity of Figs. 4, 5 and 6 to Figs. 1, 2, 3 wherein patient had been on total starvation.

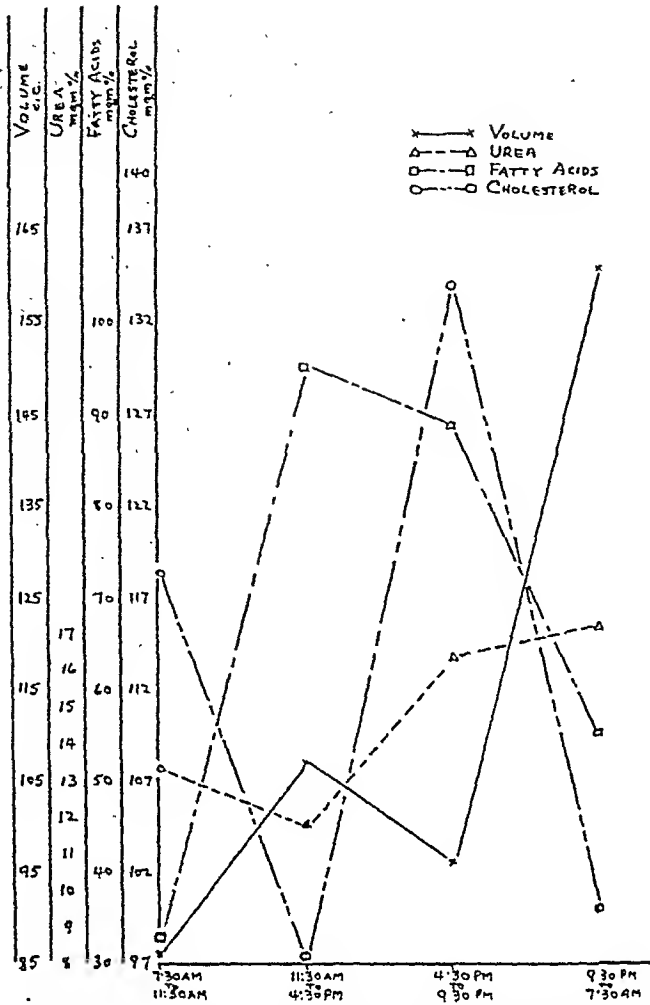


Fig. 5. Biliary urea, fatty acids, cholesterol and total volume for 24 hour period, patient fed 400 grams of glucose.

accurate methods were available to us for such studies on small quantities of bile. Conceivably these substances may have altered the correlations presented. However, the inference from these correlations, incomplete though they be in the above-mentioned detail, is that bile as it is excreted by the liver is a physico-chemical system and that its constituent elements are in a state of equilibrium. With the well-known possibilities of differential absorption of water and various constituents of bile from it through semi-permeable membranes, and with the fact that various elements in the bile are probably in equilibrium with similar elements in the blood stream (15) and may be influenced in turn by alimentary variations of these elements (16), the correlations from our experiments suggest that the mechanism of gall stone formation is one of simple precipitation from a solution the equilibrium of whose constituents has been altered by a shift in the concentration of one or more of its constituents due to such differential absorption (17.)

In a previous paper (2) we showed that carbohydrate feeding had no effect on the total volume of liver bile. In a similar manner, it can be seen from Table II and Figs. 4, 5 and 6, that feeding 400 grams of glucose did not alter the chemical composition of liver bile, nor did it affect the correlations of the determined constituents extant in liver bile excreted

with the patient on total starvation. The specimens analyzed in these glucose feeding experiments were collected, on four separate test days, in the manner previously described for the fasting experiments. No Fehling-reducing substance was found in any specimen of bile after carbohydrate feeding.

### SUMMARY

1. The results of simultaneous quantitative determinations of anions, cations, cholesterol, fatty acids, and urea in fractionally-collected specimens of human liver (fistula) bile are given, the subject having a total external fistula and no gall bladder or evidence of liver damage or infection, and being on total starvation. These values are compared with similar values in specimens obtained after high carbohydrate feeding, it being shown that such feeding does not alter the quantitative composition of liver bile nor the relationships existing between its various constituents. This is confirmatory of previous work (2) showing that carbohydrate feeding exerted no effect on the total volume of liver bile excreted.

2. The correlations noted between various constituent groupings in liver bile suggest that bile is a physico-chemical system in equilibrium and lend

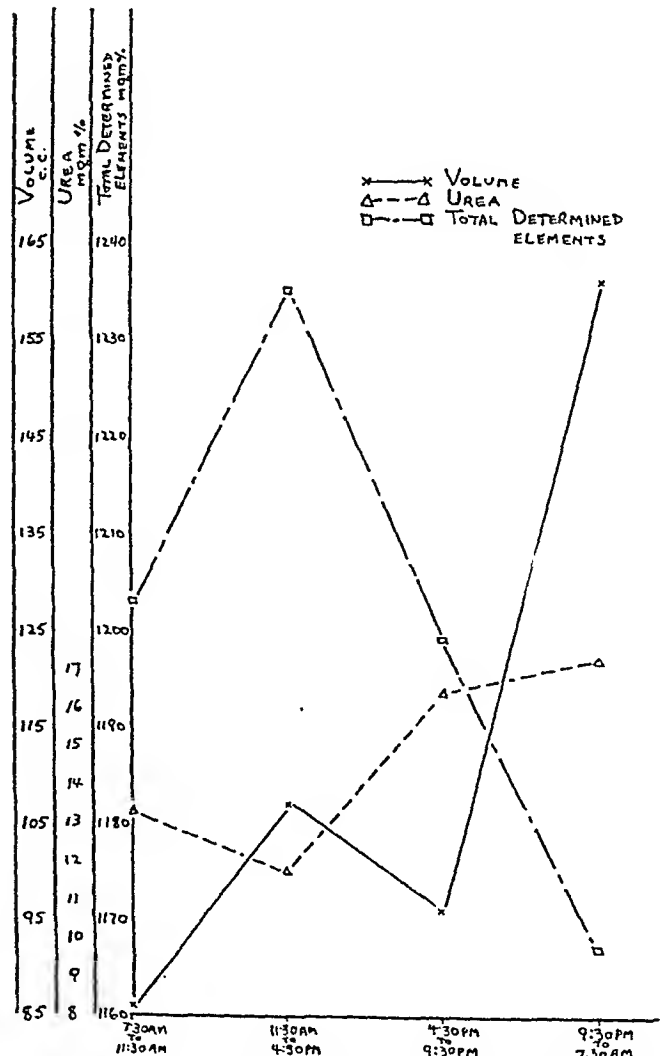


Fig. 6. Relation of all determined biliary elements (see Table II), bile volume and urea for 24 hour period, patient fed 400 grams of glucose.



support to the precipitation mechanism theory of gall stone formation.

It was our intention to continue these studies with various other food factors, cholagogues, and drugs. The patient, however, previously quite cooperative in all these experiments, became insistent on having the fistula closed just after the above-detailed studies were completed. This was successfully performed by one of us (B. K.) One year thereafter, there is no evidence of fistula, she has clinically adequate amounts of bile in her stool (she no longer takes any bile or bile preparation orally), has gained 20 pounds, is

quite well and is doing her regular work as a factory worker as well as her own housekeeping. Three biopsies from the liver, taken at the time of the closure, showed completely normal histology; in particular was there not the slightest evidence of portal inflammatory or fibrotic changes, or duct dilatation, or hepatic cord or Kupfer cellular hyperplasia or atrophy.

We should like to express our thanks to Dr. A. C. Ivy of Northwestern University Medical School in Chicago for valuable suggestions during various of the experiments in this series.

## REFERENCES

1. Zuckerman, I. C., Kogut, B. and Jacobi, M.: *Am. J. Dig. Dis.*, 6:183, 1939.
2. Jacobi, M., Zuckerman, I. C. and Kogut, B.: *Am. J. Dig. Dis.*, 6:270, 1939.
3. Pfaff, F. and Blach, A. W.: *J. Exp. Med.*, 2:49, 1891.
4. Paton, D. N. and Balfour, J. M.: Reports from the Laboratory of the Royal College of Physicians of Edinburgh, 3:191, 1891.
5. Sobel, A. E., Yuska, H. and Cohen, J.: *J. Biol. Chem.*, 118:443, 1937.
6. Volhard, J., as modified by Harvey, S. C.: *Arch. Int. Med.*, 6:12, 1910.
7. Stadie, W. C. and Ross, E. C.: *J. Biol. Chem.*, 65:735, 1925.
8. Weinbach, A. P.: *J. Biol. Chem.*, 110:95, 1935.
9. Klein, B. and Jacobi, M.: *Ind. and Engin. Chem.*, anal. ed., 12:687, 1940.
10. Kuttner, T. and Lichtenstein, L.: *J. Biol. Chem.*, 86:671, 1930.
11. Fiske, C. H.: *J. Biol. Chem.*, 47:59, 1921.
12. Bloor, W. R., Pelkan, K. F. and Allen, D. M.: *J. Biol. Chem.*, 62:191, 1922.
13. Bloor, W. R.: *J. Biol. Chem.*, 77:53, 1928.
14. Peters, J. P. and Van Slyke, D. D.: *Quantitative Clinical Chemistry*. Williams & Wilkins Co., Baltimore, ed., Vol. 2, p. 290, 1932.
15. Gamble, J. L. and Melver, M. A.: *J. Exp. Med.*, 48:849, 1928.
16. Wilkie, A. L. and Doubilet, H.: *Arch. Surg.*, 26:110, 1933.
17. McMasters, P. D.: *J. Exp. Med.*, 40:25, 1924.
18. Arndt, H. J.: *Ztschr. f. d. gesamte. exp. Mediz.*, 54:390, 1927.
19. Rous, P., McMasters, P. D. and Drury, D. R.: *J. Exp. Med.*, 39:77, 1924; *Proc. Soc. Exp. Biol. and Med.*, 20:315, 1922.

# The Influence of Single and Multiple B Complex Deficiencies upon the Motility of the Gastro-Intestinal Tract

By

GUSTAV J. MARTIN, MARVIN R. THOMPSON

and

JOSE DE CARVAJAL-FORERO

NEW YORK, NEW YORK

THE role of B complex factors in the control of secretion and motility of the gastro-intestinal tract has remained obscure despite the work of many investigators (1-25.) The problem has assumed clinical significance with the observations in humans (16-25) of a syndrome associated with a deficiency of some member or members of the B complex. LePore and Golden (25) state that patients showing the gastro-intestinal syndrome associated with B complex deficiency also show a flat oral-dextrose tolerance curve. Russell and Nasset (15) associated pantothenic acid deficiency with decreased absorption of carbohydrates. These two reports (15, 25) led us to focus our attention on pantothenic acid and inositol.

## PROCEDURE

Young dogs (a total of 30 animals), six to eight weeks old, were used throughout these studies. The animals were placed on a highly purified synthetic diet of the following composition:

|                     |      |
|---------------------|------|
| Vitamin Free Casein | 18.0 |
| Sucrose             | 67.0 |
| Butter Fat          | 9.0  |
| Salts               | 4.0  |
| Cod Liver Oil       | 2.0  |

The salt mixture was the regular U.S.P. salt mixture. Vitamin free casein was used throughout.

This diet was fed ad libitum. The vitamin supplements were given in white crocks with a small amount of glucose (1 gram) added so that the dog consumed the material immediately. To facilitate immediate consumption of the vitamin supplements the water containers were removed for an hour before and after the supplements were given. To further insure adequate dosage, intramuscular administrations were used before the dogs were taken for roentgenological examination. The daily doses of the B complex vitamin were:

|                        |     |     |                   |
|------------------------|-----|-----|-------------------|
| Thiamine hydrochloride | 50  | ug. | per kilo. per day |
| Riboflavin             | 50  | ug. | per kilo. per day |
| Pyridoxine             | 30  | ug. | per kilo. per day |
| Choline                | 1   | mg. | per kilo. per day |
| Nicotinic Acid         | 1   | mg. | per kilo. per day |
| Calcium Pantothenate   | 50  | ug. | per kilo. per day |
| Inositol               | 0.5 | mg. | per kilo. per day |
| p-Aminobenzoic Acid    | 0.5 | mg. | per kilo. per day |

Six groups of 5 dogs each were used in this study.

After the initial control fluoroscopic examination, the animals were maintained for periods in excess of two months on the various dietary regimens, and were then examined weekly for manifestations of altered gastro-intestinal function. Barium sulfate was given by means of a catheter and examinations made roentgenologically every hour for six hours, and again twenty-four hours later. Radiograms were taken after each fluoroscopic examination.

Group 1. These animals (5 dogs) were given the basic diet plus thiamine (50 ug. per kilo.) and riboflavin (50 ug. per kilo.) After two months on the diet, these animals showed by radiological examination the development of a characteristic gastro-intestinal syndrome.

Peristalsis of the stomach was shallow with a cycle of one wave every thirty seconds. Opening of the pylorus occurred at the end of twelve minutes. There was a slight forward and backward surge of the meal. The stomach emptied rather rapidly. The distribution of the meal throughout the small intestine was irregular. There were several loops of the small intestine markedly dilated, while others were uneven in caliber. There were several isolated loops retaining barium.

Barium had reached the splenic flexure of the colon at the end of two hours. There was marked segmentation of the entire colon (Fig. I, 1). These discreet masses were wider than usual and of a fusiform contour. There was hypomotility of the colon. Although the barium had reached the rectum at the end of six hours, there was still some barium retained in the sigmoid and rectum at the end of twenty-four hours.

The entire series gave the impression of a diminution in the contents of the tract after the first hour, suggesting interference with the normal secretions. The picture is one of hypermotility of the small intestine; of marked segmentation and hypomotility of the colon. The radiological picture of the gastro-intestinal tract of dogs on a diet deficient in all of the B complex factors does not differ significantly from that of dogs (group 1) receiving thiamine and riboflavin but no other B complex factors.

Group 2. These animals (5 dogs) were given the basic diet plus supplements of thiamine hydrochloride (50 ug. per kilo.), riboflavin (50 ug. per kilo.), pyridoxine (30 ug. per kilo.), calcium pantothenate (50 ug. per kilo.) and choline (1.0 mg. per kilo.) The diet was therefore deficient in nicotinic acid, inositol, and p-aminobenzoic acid. After two months on this diet, these animals showed by radiological examination the development of a characteristic gastro-intestinal syndrome.

There was a very poor peristalsis of the stomach in this group. Occasional regurgitation was observed. No barium had passed into the duodenum at the end of fifteen minutes, suggesting pylorospasm. The distribution throughout the small intestine was very irregular; several loops were dilated, while others were markedly decreased in caliber. There was little if any motility of the intestine. Gas was seen mixed with the barium meal. Considerable dilatation and segmentation of the terminal loops of the ileum was noted (Fig. I, 2.) The colon was fairly well filled at the end of six hours but presented in its proximal end (caecum, ascending and right transverse) a very marked and persistent narrowing of these structures. There was ileal stasis at the end of six hours, suggesting spasm at the ileo-cecal valve.

The entire series gave the impression of marked hypomotility with changes in the caliber of the intestine from enlarged loops to ribbon-like structures. Spasm at the pylorus and ileo-caecal valve was noted. A mixing of gas with the barium meal occurred. The marked narrowing of the lumen in the middle third of the small intestine suggested hypertonicity.

Group 3. These animals received the basic diet plus

supplements of thiamine hydrochloride (50 ug. per kilo.), riboflavin (50 ug. per kilo.), pyridoxine (30 ug. per kilo.) and calcium pantothenate (50 ug. per kilo.). After two months on this regimen, these animals showed by radiological examination the development of a characteristic gastro-intestinal syndrome.

The peristalsis of the stomach was active with good amplitude and a cycle of four waves per minute. The pylorus did not open, however, until twelve minutes had elapsed. There was a forward and backward surge in the duodenum. The distribution throughout the small intestine was very irregular. The meal passed rapidly through the jejunum and accumulated in the ileum in segmented loops markedly distended. These loops showed activity, but the barium moved back and forth without any forward progress. The amount of barium distributed throughout the small intestine seemed diminished, suggesting interference with intestinal secretions. The barium reached and began to pass through the ileo-caecal valve at the end of the second hour; the passage was rather slow, and the colon did not fill completely until the end of six hours (Fig. I, 3.) There were several scattered loops of the small intestine remaining filled at the end of five hours. The colon showed segmentation and there was a residue in the sigmoid and rectum at the end of twenty-four hours.

This series gave the impression of hypermotility of the jejunum with abnormal segmentation of the ileum and colon. Diminution of the intestinal contents was noted. The radiological picture of the gastro-intestinal tract of animals in Groups 2 and 3 differs only in that the latter shows a hypermotility throughout the intestine, which we attributed to the superimposed choline deficiency.

Group 4. These animals received the basic diet plus supplements of thiamine (50 ug. per kilo.), riboflavin (50 ug. per kilo.), calcium pantothenate (50 ug. per kilo.), choline (1.0 mg. per kilo.) and nicotinic acid (1.0 mg. per kilo.) After two months on this regimen, these animals showed by radiological examination the development of a characteristic gastro-intestinal syndrome.

Peristalsis of the stomach in this group was very slow and shallow. At the end of fifteen minutes no barium had passed into the duodenum, and there was some gastric residue at the end of four hours (Fig. I, 4.) The distribution of the meal throughout the small intestine was uniform, although its progress was very slow, no barium having passed into the colon at the end of six hours. The entire small intestine seemed completely filled; some of the loops were markedly dilated. There was a considerable amount of gas mixed with the barium. There were isolated loops in which there was a surge back and forth without forward progress.

The radiological examination of the gastro-intestinal tracts of the animals in this group gave the impression of marked hypomotility. The enlargement of the lumen of the intestine suggested hypotonicity. There was spasm at the jejunum and ileo-caecal valve. Large amounts of gas were mixed with the barium meal. Fluid levels were observed. In this set the pyridoxine deficiency coexisting with one of inositol alters the roentgen picture to the extent of causing a change from hypertonicity to hypotonicity.

Group 5. These animals received the basic diet plus supplements of thiamine (50 ug. per kilo.), riboflavin (50 ug. per kilo.), pyridoxine (30 ug. per kilo.), choline (1 mg. per kilo.), nicotinic acid (1.0 mg. per kilo.), calcium pantothenate (50 ug. per kilo.), inositol (0.5 mg. per kilo.), and p-aminobenzoic acid (0.5 mg. per kilo.) With the exception of biotin, this represents the entire group of B complex members available

in crystalline form. The animals may be said to be on a nutritionally adequate, highly purified synthetic diet. After two months on this regimen, these animals showed by radiological examination a normal gastro-intestinal tract.

Peristalsis of the stomach in this group was very active with excellent amplitude and a cycle of a wave every twelve seconds. Peristaltic waves commenced in



Fig. 1—4 hours after barium meal.

Group 1. Marked segmentation of colon. Isolated loops. Narrowing of lumen of terminal ileum. Diminution of intestinal contents. Group 2. Segmentation. Dilatation of some loops and marked narrowing of others. Marked constrictions. Group 3. Isolated loops. Dilatation of terminal loops of ileum. Marked segmentation of colon. Group 4. Irregular distribution. Marked segmentation. Dilatation and narrowing of loops. Gas and fluid levels. Slow progress of Barium. Group 5. Regular distribution through terminal ileum and proximal colon. Group 6. Isolated loops. Segmentation of colon. Diminution of intestinal contents.

the preantral region of the stomach and traveled forth rhythmically. Barium began to pass into the duodenum at the end of five minutes. The distribution throughout the small intestine was regular. The lumen of the intestine seemed uniform, and the propulsion of the meal forward was effected by regular peristaltic and tonus waves. The barium reached the ileo-caecal valve at the end of three hours. The colon was completely filled at six hours (Fig. I, 5.) There was in some subjects a collection of gas in the distal part of the colon.

The animals in this group gave the impression of normality, with normal emptying of the stomach, with regular distribution of barium throughout the gastro-intestinal tract, with a complete absence of dilatations, constrictions and segmentations and with good peristalsis throughout. Thus, on a purified diet containing eight B complex factors, the dog is able to maintain a normal gastro-intestinal, radiological picture.

Group 6. These animals received the basic diet plus supplements of thiamine (50 ug. per kilo.), riboflavin (50 ug. per kilo.), pyridoxine (30 ug. per kilo.), choline (1.0 mg. per kilo.), inositol (0.5 mg. per kilo.), nicotinic acid (1.0 mg. per kilo.) and p-aminobenzoic acid (0.5 mg. per kilo.) This represents a pure calcium pantothenate deficiency, the first of the single deficiencies studied in dogs.

Peristalsis of the stomach in this group was very slow and shallow. No barium had passed into the duodenum at the end of twenty minutes, suggesting pylorospasm. The distribution throughout the small intestine was very irregular. There were several isolated loops in the jejunum and others were reduced in caliber. The ileum was likewise markedly segmented and some of the loops were enlarged. The impression was gained that there was a diminution of the intestinal contents. There were considerable amounts of gas in the intestine. Barium began to pass into the colon at the end of the second hour, and its distribution here was likewise irregular with marked segmentations. The colon was completely filled at the end of four hours (Fig. I, 6.) There was a residue in the sigmoid and rectum at the end of twenty-four hours.

The gastro-intestinal tract of the animals in this group gave the impression of marked hypomotility on radiological examination. The segmentation of the loops and the changes in size of the lumen from very narrow to markedly dilated, as well as the motion seen within these discreet loops, suggested a hypertonic segmentation. There was marked hypomotility of the colon as well as marked segmentation and pylorospasm. The animals in this set show the results of a deficiency of a single factor of the B complex (pantothenic acid) on the gastro-intestinal tract.

## DISCUSSION

From a consideration of the radiological findings it is our opinion that in each of the sets, other than set 5 (which received both inositol and pantothenic acid) there are features in common suggesting that the two factors, inositol and pantothenic acid, are both associated with the maintenance of gastro-intestinal normalcy. That other factors, such as pyridoxine, may influence the general picture is illustrated by the hypotonicity of sets 1 and 4. The striking similarity of pantothenic acid and inositol deficiencies in their effect on the gastro-intestinal tract is to be emphasized and suggests the presence of an interdependence

of the two factors. The same features characterize the picture if either is absent from the diet. These features are:

1. Increased gastric emptying time with pylorospasm.
2. Marked segmentation of both the small and the large intestine.
3. General picture of hypertonicity with hypomotility.
4. Alternation of ribbon-like segments with dilated loops.
5. Frequent formation of gas.
6. Fluid levels.

These findings and conclusions are in part substantiated by, and in part contradicted by, clinical and experimental data relating to the role of the B complex in gastro-intestinal function.

The literature on thiamine indicates that the gastro-intestinal changes associated with a deficiency of this vitamin have not been completely demonstrated as having direct origin in a deficiency of thiamine. Alvarez et al (2) and Sure et al (3) have been unable to demonstrate any change in gastric secretion due to a lack of thiamine. Williams and Spies (4) state that thiamine is essential for the normal functioning of the gastro-intestinal tract. In some cases, the motility was abnormal. On a diet deficient in all members of the B complex our dogs developed abnormalities of the gastro-intestinal tract, which are not significantly altered by the addition of thiamine to the diet. Sparks and Collins (5) have reported that thiamine deficiency in rats causes a marked increase in the volume of the colon. This demonstrates that thiamine has some direct action in maintaining intestinal tone. We observed no effect of thiamine in our radiological examinations. Chatterjee (6) studied the motor functions of the intestine in the presence of a thiamine deficiency. In the vitamin-deprived animals there was a definite decrease in the amplitude, the number and the intensity of intestinal contractions and responses to pilocarpine, atropine, nicotine and barium chloride. Recently, it has been reported (7) that thiamine increased peristalsis and that rate of tonus loss was retarded within ten minutes after the addition of thiamine to intestine isolated from thiamine deficient animals. It is quite possible that a pure thiamine deficiency would manifest itself in gastro-intestinal changes, provided the other seven available factors of the B complex were administered.

Street and Cowgill (8) studied the effect of riboflavin deficiency on dogs. Diarrhea in these animals manifested itself in the collapse stage but was not present during the prodromal period. Again, addition of riboflavin to the diet of dogs deficient in the B complex was without effect even in the presence of thiamine. Our Group 1 received thiamine and riboflavin as diet supplements, and the roentgenological studies showed no marked difference from those of animals on a diet deficient in the entire B complex.

Pyridoxine, Vitamin B<sub>6</sub>, was found by Borson and Mettier (9) to cure the hypochromic microcytic anemia produced in dogs, but they reported no manifestation of abnormal gastro-intestinal function, mentioning only listlessness and asthenia as symptoms. We demonstrated a pyridoxine effect in our studies inasmuch as it (Groups 1 and 4) modified the

gastro-intestinal picture associated with inositol or pantothenic acid deficiency.

Indigestion and diarrhea have long been known as characterizing pellagra. Wheeler and Goldberger (10) reported diarrhea as a prominent feature of the effects of a black tongue diet in dogs. Crandall et al (11) state that a P-P factor (nicotinic acid, nicotinamide or a substance capable of replacing it) is essential for the maintenance of normal gastro-intestinal motility. Animals on a nicotinic acid deficient, black tongue diet, showed hypermotility of the gastro-intestinal tract. In three dogs barium reached the rectum in 2 hours. Thiamine and riboflavin were reported ineffective in functional digestive disturbances. The effect of nicotinic acid in correcting hypermotility is in complete harmony with our findings in normal dogs (1) which clearly show that this acid decreases peristalsis in both the stomach and small intestine. We have not noted any marked effect of nicotinic acid deficiency in dogs, comparing our Groups 2 and 4. It is to be noted that we have again not produced a pure nicotinic acid deficiency in dogs receiving the other eight members of the B complex. We reserve final judgment on the role of nicotinic acid in gastro-intestinal motility.

Calcium pantothenate deficiency has been produced in dogs by several groups of workers. Morgan and Simms (12) noted bloody diarrhea in their dogs on diets deficient in filtrate factors. McKibbin et al (13) tried an experiment supplying pyridoxine, as well as thiamine, riboflavin, and nicotinic acid along with the purified diet. They found that pantothenic acid and another alkali labile factor, as well as factor W, were needed for growth of young mongrel puppies. The test periods were short, and they reported no gastro-intestinal abnormalities. Fouts et al (14) gave supplements of thiamine, riboflavin, nicotinic acid and pyridoxine and found that all their animals developed diarrhea within 7 to 66 days. It was intermittent in character but became severe and often bloody before death. Decrease in appetite was especially marked during exacerbations of diarrhea. Vomiting occurred frequently. At autopsy the liver of each dog appeared to be fatty. One animal had superficial ulcerations of the gums, another had numerous shallow ulcers and hemorrhages in the ileum, and one dog had a penetrating ulcer on the lesser curvature of the stomach as well as numerous superficial ulcers scattered throughout this organ and the first portion of the duodenum. Russell and Nasset (15) have studied the effects of various vitamin supplements and of whole yeast on the digestion and absorption of carbohydrates. A distinct stimulatory effect of fresh yeast on gastro-intestinal motility was noted. The increased motility was accompanied by increased rates of digestion and absorption of carbohydrate. Additional amounts of thiamine, riboflavin, nicotinic acid and pyridoxine had no effect, but these authors present evidence indicating that crystalline pantothenic acid is responsible for at least part of the yeast effect. Our results point to two factors, inositol and pantothenic acid. A deficiency of either factor

produces the same picture, suggesting a similarity of action. The gastro-intestinal abnormalities produced by inositol or pantothenic acid deficiency are: increased gastric emptying time with pyloro-spasm, ribbon-like appearance of the small intestine, hyper-tonicity and marked segmentation. Our Group 5, receiving all eight factors of the B complex, showed essentially normal gastro-intestinal motility.

Inositol has been reported (1) to be a factor in the control of gastro-intestinal motility in mice and to be a factor influencing motility in the normal animal (1.) It has now been shown to be a vitamin, lack of which produces a picture similar to that of a pantothenic acid deficiency.

The apparent normality of the gastro-intestinal tract of our Group 5 indicates that with eight of the nine B complex factors, in the absence of biotin, a complete diet is attained.

The effect of choline deficiency on the gastro-intestinal tract of the dog remains to be considered. It is impossible to eliminate this compound as a potential factor from our present results. There would seem to be some reason to conclude that it may be active in increasing secretion of fluids into the gastro-intestinal tract. Those groups on diets deficient in choline (Groups 1 and 3) seemed to show a diminished gastric or intestinal content as contrasted to those receiving choline. We are now conducting experiments to check the role of choline in the maintenance of gastro-intestinal motility and function.

Heublein and his coworkers (26) have recently described the syndrome in dogs associated with deficiency of the entire B complex. The radiological picture noted by these investigators is identical with that described herein. They, too, eliminated thiamine, riboflavin and nicotinic acid as factors of vital importance in the syndrome. As we demonstrate here, the syndrome observed is that of a pantothenic acid-inositol deficiency.

The clinical aspects of this problem have received extensive consideration. Mackie (15) first noted in the small intestine changes of a functional nature, in non-tropical sprue. Subsequently similar changes were observed in chronic idiopathic steatorrhea (17), in ulcerative colitis (18) and in tropical sprue (19), as well as in a variety of conditions, nephrosis and diabetes insipidus (20), icterus (21), diseases of mesenteric lymphatics and intra-abdominal cancer, etc. Elsom et al (22), maintained patients on a diet deficient in the B complex and studied among other things the gastro-intestinal tract. They noted after one week on the diet a mild anorexia, which ultimately became extreme. Abdominal distension and constipation were marked. Mild soreness of the tongue was an occasional complaint. As the deficiency became more pronounced, nausea and vomiting were frequent, and during the last few days on the diet abdominal pain was noted. Appetite returned promptly following administration of thiamine. This return of appetite was not associated with any change in the other gastro-intestinal symptoms except that abdominal pain disappeared. Toward the end of the second week of thiamine therapy, appetite again decreased, and, in

spite of continued administration of thiamine and addition to riboflavin, did not again return to normal until yeast was given. Roentgen-examination of the gastro-intestinal tract at the termination of the deficiency-diet period showed no abnormality except some increased caliber of jejunal loops. After the subject had received thiamine for 18 days there was delayed gastric emptying and slight delay in small bowel motility. Increased caliber of the jejunal loops was still evident. Riboflavin did not significantly alter these findings. Following the administration of yeast, however, there was marked improvement in the small intestinal motility, the head of the barium column having reached the hepatic flexure four hours and forty minutes after the ingestion of the barium, while under the thiamine and riboflavin therapy a comparable film was not observed until six hours after the start of the examination. A slight delay in gastric emptying time persisted. These results are in complete harmony with our own observations. Recently, Mackie (23) has stated that the deficiency pattern in the small intestine does not respond to thiamine, riboflavin or nicotinic acid and consequently must depend on some factors of the B complex other than these substances. He points out that the pattern is accompanied by interference with the function of absorption and may therefore contribute to the establishment of an ascending spiral of progressing deficiency disease. Golden (24) and Lepore and Golden (25)

discuss the clinical aspects of this problem. They report a flat oral-dextrose tolerance curve in their patients, indicating a slow absorption of dextrose from the gastro-intestinal tract. This suggests the effect of pantothenic acid on carbohydrate absorption as reported by Russell and Nasset (15.)

It has been shown that factors other than thiamine, riboflavin, pyridoxine and nicotinic acid are responsible for normal gastro-intestinal motility. We have demonstrated that pantothenic acid and inositol are the factors involved.

### SUMMARY

A deficiency of either pantothenic acid or inositol produces an abnormal gastro-intestinal picture in the dog which is characterized by:

1. Increased gastric emptying time with pylorospasm.
2. Marked segmentation of both the small and the large intestine.
3. General picture of hypertonicity with hypomotility.
4. Alternation of ribbon-like segments with dilated loops.
5. Frequent formation of gas.
6. Fluid levels.

It is suggested that as a deficiency of either pantothenic acid or inositol produces this picture, therapeutically, both vitamins should be administered together.

### REFERENCES

1. Martin, Gustav J., Thompson, Marvin R. and de Carvajal-Forero, Jose: The Influence of Inositol and Other B Complex Factors Upon the Motility of the Gastro-Intestinal Tract. *Am. J. Dig. Dis.*, 8:290, 1941.
2. Alvarez, W. C., Pilcher, F., Foley, M. A., Mayer, A. and Osterberg, A. E.: The Effects on Gastric Juice of Deprivation of Vitamin B<sub>1</sub>. *Am. J. Dig. Dis. and Nutrit.*, 3:102, 1937.
3. Sure, B. and Harrelson, R. T.: Enzymic Efficiency in Avitaminosis. *Am. J. Dig. Dis. and Nutrit.*, 4:177, 1937.
4. Williams, R. R. and Spies, T. D.: Vitamin B<sub>1</sub>. New York, MacMillan, 1938.
5. Sparks, M. I. and Collins, E. N.: The Role of Vitamin B<sub>1</sub> in the Tonus of Large Intestines. *Am. J. Dig. Dis. and Nutrit.*, 2:618, 1935.
6. Chatterjee, D. D.: Intestinal Motility in Avitaminosis B and in Starved Animals. *Indian J. M. Res.*, 23:191, 1935.
7. Dick, McDonald and Heger, J. Roy: The Effect of Thiamin on the Intestine of the B<sub>1</sub> Deficient Rat. *Am. J. Physiol.*, 132:636, 1941.
8. Street, R. R. and Cowgill, G. R.: Acute Riboflavin Deficiency in the Dog. *Am. J. Physiol.*, 125:323, 1939.
9. Borson, H. J. and Mettler, S. R.: Relief of Hypochromic Microcytic Anemia in Dogs with Synthetic Vitamin B<sub>6</sub>. Influence of Filtrate Factors. *Proc. Soc. Exp. Biol. and Med.*, 43:429, 1940.
10. Goldberger, J. and Wheeler, G. A.: Study on Endemic Pellagra. *U. S. Pub. Health Repr.*, 43:2645, 1928.
11. Crandall, L. A., Chesley, F. F., Hansen, D. and Dunbar, J.: The Relation of P-P Factor to Gastro-Intestinal Motility. *Proc. Soc. Exp. Biol. and Med.*, 41:472, 1939.
12. Morgan, A. F. and Simms, H. D.: Greying of Fur and Other Disturbances in Several Species Due to a Vitamin Deficiency. *J. Nutrition*, 19:233, 1940.
13. McKibbin, J. M., Black, S. and Elvehjem, C. A.: The Importance of Vitamin B<sub>6</sub> and Factor W in Nutrition of Dogs. *Am. J. Physiol.*, 130:365, 1940.
14. Fouts, P. J., Helmer, O. M. and Lepkovsky, S.: Factor 11 Deficiency in Dogs. *J. Nutrition*, 19:393, 1941.
15. Russell, R. A. and Nasset, E. S.: The Effects of Various Supplements and of Whole Yeast on the Digestion and Absorption of the Carbohydrate Complete Diet. *J. Nutrition*, 22:287, 1941.
16. Mackie, T. T.: Non Tropical Sprue. *M. Clin. North America*, 17:165, 1933.
17. Snell, A. M. and Camp, J. D.: Chronic Idiopathic Steatorrhea, Roentgenologic Observations. *Arch. Int. Med.*, 53:615, 1934.
18. Mackie, T. T. and Pound, R. E.: Changes in the Gastro-Intestinal Tract in Deficiency States with Special Reference to the Small Intestine. *J. A. M. A.*, 104:613, 1935.
19. Mackie, T. T., Miller, D. K. and Rhoads, C. P.: Sprue. *Am. J. Trop. Med.*, 15:571, 1935.
20. Pendergrass, E. P., Ravdin, I. S., Johnston, C. J. and Hodes, P. J.: Studies of the Small Intestine. *Radiology*, 26:651, 1936.
21. Gutzeit and Kuhlbaum: Ueber die Darm-motilität beim Ikterus. *München. med. Wochenschr.*, 81:1095, 1934.
22. Elsom, K., O'Shea, Lewy, F. H. and Heublein, G. W.: Clinical Significance of Experimental Human Vitamin B Complex Deficiency. *Am. J. Med. Sci.*, 200:757, 1940.
23. Mackie, T. T.: Vitamin Deficiencies and the Small Intestine. *J. A. M. A.*, 117:910, 1941.
24. Golden, Ross: Abnormalities of the Small Intestine in Nutritional Disturbances. *Radiology*, 36:232, 1941.
25. Lepore, Michael J. and Golden, Ross: A Syndrome Due to Deficiency of the Vitamin B Complex. *J. A. M. A.*, 117:918, 1941.
26. Heublein, G. W., Thompson, W. D. and Scully, J. P.: The Effect of a Vitamin B Complex Deficiency on Gastric Emptying and Small Intestinal Motility. *Am. J. Roent.*, 46:876, 1941.

### LECTURESHIP NAMED FOR DR. JULIUS FRIEDENWALD

As a memorial to the late Doctor Julius Friedenwald, an annual lectureship has been established at the school of Medicine, of the University of Maryland, Baltimore. Dr. Julius Friedenwald was for many years professor of gastro-enterology and emeritus professor at the University of Maryland at the time of his death in June, 1941.

### COMMITTEE ON MILITARY PREPAREDNESS

145 WEST 86TH STREET

NEW YORK CITY

June 8, 1942.

To the President and Governing Board  
American Gastro-Enterological Association  
Atlantic City, New Jersey.  
Gentlemen:

I have the honor to present the fourth report of your Committee on Military Preparedness (previous reports January 6, 1941, May 3, 1941, and January 25, 1942.)



1. *Gastro-Enterologists recommended for duty in the Army of the United States.* The following is a list of gastro-enterologists who have applied for approval of this Committee, with the positions for which they have been recommended:

| Name                           | Location              | Recommended as |
|--------------------------------|-----------------------|----------------|
| 1. Dr. James L. Borland        | Jacksonville, Florida | Chief          |
| 2. Dr. Rudolf Schindler        | Chicago, Illinois     | Chief          |
| 3. Dr. Jack E. Berk            | Philadelphia, Pa.     | Ass't or Chief |
| 4. Dr. William H. Folk         | Spartanburg, S. C.    | Assistant      |
| 5. Dr. Irving Gray             | Brooklyn, N. Y.       | Chief          |
| 6. Dr. John B. D'Albora        | Brooklyn, N. Y.       | Chief          |
| 7. Dr. Saverio C. Franco       | Brooklyn, N. Y.       | Assistant      |
| 8. Dr. Bernard D. Rosenak      | Indianapolis, Ind.    | Chief          |
| 9. Dr. C. Joseph Miller        | Philadelphia, Pa.     | Chief          |
| 10. Dr. Emanuel M. Rappaport   | Jamaica, L. I.        | Assistant      |
| 11. Dr. Philip Fieman          | Philadelphia, Pa.     | Assistant      |
| 12. Dr. Fred E. Manulis        | Brooklyn, N. Y.       | Assistant      |
| 13. Dr. Samuel Morrison        | Baltimore, Md.        | Chief          |
| 14. Dr. Crawford F. Barnett    | Atlanta, Ga.          | Chief          |
| 15. Dr. Lester M. Morrison     | Philadelphia, Pa.     | Chief          |
| 16. Dr. Marcus H. Sugarman     | Detroit, Mich.        | Assistant      |
| 17. Dr. Edward E. Levine       | Detroit, Mich.        | Assistant      |
| 18. Dr. Paul M. Schwartz       | Poughkeepsie, N. Y.   | Assistant      |
| 19. Dr. Jerome S. Levy         | Little Rock, Ark.     | Chief          |
| 20. Dr. Franklin W. White      | Boston, Mass.         | Chief          |
| 21. Dr. Manfred Kraemer        | Newark, N. J.         | Chief          |
| 22. Dr. Henry A. Brocksmitth   | Tulsa, Oklahoma       | Chief          |
| 23. Major Donald B. Chamberlin | Lawson Gen'l Hosp.    | Chief          |
| (for record only)              |                       |                |
| 24. Dr. Harold K. Moss         | Cincinnati, Ohio      | Chief          |
| 25. Dr. Samuel Myerson         | New York City         | Chief          |
| 26. Major Joseph Bank          | Phoenix, Arizona      | Chief          |

Dr. Max Einhorn of New York City, although 80 years of age, has also offered his services to The Surgeon General of the Army.

2. *Procedure to be followed by applicants for obtaining recommendation of this Committee:*

A. Non-members of the American Gastro-Enterological Association.

1. Make application for a commission in the Army of the United States.
2. Prepare a statement of experience and qualifications (including date of birth) and submit in duplicate to Chairman of this Committee.
3. Request that the member of this Committee who is located nearest to applicant, review the applicant's qualifications and send to Chairman of this Committee a specific statement as to whether applicant is qualified to act as Chief or only as Assistant in a Section of Gastro-Enterology in an Army General Hospital.

B. Members of the American Gastro-Enterological Association.

1. As above in A 1.
2. Write a letter to Chairman of this Committee stating that applicant desires to serve as a gastro-enterologist in the Army of the United States.

3. *Procedure followed by this Committee in recommending applicant to higher authority.* Individual recommendations as to qualifications of applicants are sent to Dr. R. G. Leland in Chicago, who is now Supervisor, Consultant Office, Procurement and Assignment Service. At intervals, consolidated lists of recommended physicians are sent direct to The Surgeon General's Office.

4. *Sections of Gastro-Enterology now operating in U. S. Army General Hospitals.* In addition to the sections of gastro-enterology permanently established at the fixed General Hospitals and headed by regular army personnel,

sections of gastro-enterology are operating in cantonment general hospitals. To date your Chairman has heard from the following:

Lawson General Hospital, Atlanta, Georgia, Maj. D. T. Chamberlin, Chief; Tilton General Hospital, Fort Dix, N. J., Captain J. E. Berk, Chief; Billings General Hospital, Fort Benjamin Harrison, Ind., Lt. G. A. Boylston, Chief.

On April 11, 1942, the gastro-intestinal section at the Tilton General Hospital was visited and found to be admirably organized and operated.

*It is again requested that all gastro-enterologists assigned to active duty as such, notify the Chairman of this Committee so that the record may be kept as complete as possible.*

5. *Cooperation with Liaison Committee from Advisory Board for Medical Specialties.* On March 12, 1942, a letter was received from Dr. B. R. Kirklin of the Mayo Clinic on behalf of a liaison committee from the Advisory Board for Medical Specialties requesting information concerning available gastro-enterologists both diplomates and those with limited experience. It was particularly desired to have the number of gastro-enterologists divided according to various age groups and classified as grade 2, 3, or 4. With the assistance of Dr. A. F. R. Andresen, Chairman of the Advisory Committee on Gastro-Enterology of the American Board of Internal Medicine, and of Dr. Victor C. Myers, Chairman of the Regional Committee of the American Gastro-Enterological Association, both members of this Committee, Dr. Kirklin was given all the information available as of April 24, 1942.

6. *Formal Training of Gastro-Enterologists.* In the course of preparing the report mentioned in the preceding paragraph (paragraph 5), it became evident that no "approved institutions" are at the present time giving formal training in gastro-enterology to candidates for certification in that specialty. This Committee believes that the present is an excellent opportunity to suggest to the appropriate qualifying board that service in a section of gastro-enterology in an army general hospital may properly be regarded as the equivalent of an equal period of training in an "approved institution."

7. *Gastroscoipists in the Army of the United States.* On February 16, 1942, and again on May 5, 1942, your Committee transmitted to General C. C. Hillman, Chief of Professional Services Division of The Surgeon General's Office, lists of qualified gastroscoipists either already in the military service, or applying for admission thereto. In all, a total of 28 names was submitted together with a statement of the training, experience, and competence of each individual listed. This Committee is indebted to Dr. Chevalier Jackson of Philadelphia, Pa., Dr. H. J. Moersch of Rochester, Minn., and Dr. Rudolf Schindler of Chicago, Ill., for assistance in the compilation of this material.

8. *Gastroscoipists in the United States Navy.* On May 25, 1942, your Committee transmitted to Rear Admiral Ross T. McIntire, Surgeon General of the U. S. Navy, a list of 5 qualified gastroscoipists either already in the U. S. Naval Reserve or applicants for enrollment therein. Admiral McIntire replied on May 28th that this information would be kept in the official records of the officers concerned, and that he would be pleased to receive further data of this type whenever available.

Faithfully yours,

JOHN L. KANTOR,  
Col., Med.-Res., U. S. Army,  
Chairman.

## Gastric Secretion in the Newborn

By

M. H. F. FRIEDMAN, Ph.D.\*  
PHILADELPHIA, PENNSYLVANIA

IT is fairly well established that the stomach of the human fetus is potentially capable of secreting acid by the fifth month. Parietal cells become distinguishable towards the end of the fourth month and presumably acid can be secreted after this time (Gundolin, 1912; Taguchi, 1922; Keene et al, 1929.) The literature is replete with references to the presence of acid in the stomach of the premature and normally delivered unfed newborn infant (Leo, 1888; Pfaundler, 1899; Nathmann, 1909; Pollitzer, 1921.) In more recent investigations two points of extreme interest have been brought out—(1) the acidity of the gastric contents of the infant at birth, even before its first meal, is relatively high, and (2) the acidity of both the fasting contents and the histamine- or food-stimulated secretion decreases progressively during the first week and begins to rise again only after the tenth day.

In 55 newborn unfed infants, ages one-half to 18 hours, Hess (1913) found as much as 10 cc. of juice, the free acidity of which ranged from 10 to 90 clinical units. Taylor (1917a) reported that 6.0 cc. of juice, with a free acidity of 50 and a total acidity of 60 units, can be recovered from an infant two hours after birth. Griswold and Shohl (1925) in 25 infants, ages 15 minutes to 14 hours, reported an average of 4.5 cc. of juice being present in the stomach, with an average pH of 2.6 (range pH 1.7 to 4.4.) Ritter (1941) in 36 infants 30 minutes to 14 hours old, found the free acidity to range from 0 to 56, total acidity 11 to 84, and pH from 1.28 to 4.59.

Hess (1913) found the acidity of the fasting gastric contents to be lower during the second week than during the first few days after birth. By means of milk and water test meals administered to 30 infants, Shohl (1925) determined that gastric secretion and digestion is greater in the newborn than in later infancy. According to Cutter (1938), the acidity in response to histamine is higher during the first ten days (total acid 27.2 units, average) than during the ensuing 3 weeks (total acid 8.3 units, average.) Miller (1941) investigated a series of 50 babies during their first ten days. When the same babies were tested at intervals of several days, he found the acidity of the fasting contents to be higher on the second day than on subsequent days. By comparing a series of babies eleven to thirty days old, with a series ten or less days old, Miller concluded that the lowest values for free and total acidities are reached about the eighth to tenth day. Steinman (1936), investigating children between one month and one year, found the gastric acidity to increase during the first year and Levinson and McFate (1937) state that the acidity is low up to the third year.

Several possibilities suggest themselves to explain the highly acid gastric secretion at birth and its gradual decrease during the first week or so of life. A

secretory stimulant, passed from mother to fetus and accumulated by the latter, is likely. Exhaustion of this stored secretory stimulant would explain the falling off of the secretion during the first ten days. A gastric secretory hormone has been found in the blood of dogs (Lim and Necheles, 1926) and the gastric glands of the dog and cat respond to gastrin shortly after birth (Sutherland, 1921.) A haemopoietic substance is believed to be taken up and stored by the fetus (Wintrobe and Shumaker, 1936.) The apparent close relationship between the intrinsic factor of Castle and gastric secretion would hypothecate a substance concerned perhaps primarily with haemopoiesis and secondarily with gastric secretion. Another aspect of this relationship is suggested by Ritter (1941.) He thinks the presence in the fetus of a gastric secretory stimulant would make possible the secretion of an intrinsic factor and so "play a part in bringing the infant's erythropoietic system to a more mature level."

It is known that the plasma bicarbonate level varies directly with gastric acidity; increasing plasma bicarbonate is a potent means of facilitating gastric secretion (Delruc and Lacquet, 1934; Brown and Vineberg, 1932; Apperly and Crabtree, 1931.) The high acidity of the gastric contents at birth, however, cannot be explained by a high plasma bicarbonate due to asphyxial anoxia. On the contrary, Yllepo (1924), Marples and Lippard (1932) and others (Windle, 1940) have found the normally delivered infant to have at birth a tendency towards an acidosis.

The fetal swallowing of amniotic fluid has been suggested as a means of obtaining some nutrient by the fetus. To what extent the presence of amniotic fluid in the fetal gastro-intestinal tract may act as a gastric secretory stimulant is not known; no information is available on the secretagogue value of this fluid. In the fetal and newborn dog and cat Friedman (1936) frequently found amniotic fluid in the digestive tract and confirmed the absence of acid gastric contents when amniotic fluid had been swallowed. It may well be that swallowing of amniotic fluid by the fetus is a normal process and utilized for the purpose of neutralizing the continuous acid secretion. (This conception becomes more suggestive if certain reports in the literature that pancreatic and duodenal secretions are at a minimum at birth are confirmed.)

In the premature and the full-term newborn gastric hunger contractions occur more frequently and are more persistent and more vigorous than in older babies (Carlson and Ginsburg, 1915; Taylor, 1917b.) According to Davidsohn (1921) "the motility of stomachs in infancy increases or diminishes as the gastric acidity rises or falls." The correlation between gastric secretion and motility is obvious but no data exist on the causative agency.

\*Department of Physiology, Jefferson Medical College.  
Submitted February 5, 1942.

## The Acidity of the "Ulcer-Bearing Area" of the Duodenum in Normal Persons\*†

By

J. EDWARD BERK, M.D., M.Sc. (Med)...‡

FORT DIX, NEW JERSEY

MARTIN E. REHFUSS, M.D.

PHILADELPHIA, PENNSYLVANIA

and

J. EARL THOMAS, M.D.

PHILADELPHIA, PENNSYLVANIA

AN imposing array of clinical and experimental studies has served to establish the acid gastric juice as one of the major factors contributing to the formation and maintenance of chronic peptic ulcer. Duodenal ulcers far outrank gastric ulcers in frequency of clinical occurrence (7), yet our attention has been overwhelmingly centered on the acidity in the stomach while that in the duodenal bulb has been largely ignored. If the role of the acid factor in duodenal ulcer is to be adequately appraised, we should know something of the acidity in the ulcer-bearing duodenal bulb and, especially, the relationship which such acidity bears to that observed at the same time in the stomach. Our knowledge concerning duodenal acidity in man is by no means extensive and even less is known in this respect concerning the duodenal bulb. It is essential, therefore, that we first acquire some understanding of the situation which obtains in this area under normal conditions.

Some effort has been made to determine the reaction of the duodenal contents in normal persons (2, 14, 16, 17, 18, 19, 20, 22, 23, 24, 26, 27, 30, 31, 32, 33, 36, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 51, 52, 53, 55, 59, 61) but, so far as we could determine, only 2 investigators have concerned themselves with the important, so-called "ulcer-bearing area" of the duodenum (the bulb (24, 51.) Moreover, simultaneous analysis of the contents of the stomach and duodenum obtained without any interference with the free flow between them is imperative for any real evaluation of the relationship of the acidities in these areas. Morton's work (51) seems to be the only attempt to provide this as regards the duodenal bulb and even this is open to several criticisms. Chief among these is the uncertainty of the position of the tip of the duodenal tube throughout the period of observation, the examination of only single specimens for the most part, and the lack of pH determinations.

The acidity of the contents of the first part of the duodenum in persons without peptic ulcer was found by Morton (51) to be always low and relatively constant despite a wide variation in acidity in the stomach. We noted similar discrepancies between the acidity in the stomach and that simultaneously determined in the duodenal bulb in normal dogs (7, 8,

9). Kearney (33), studying 7 normal persons, was unable to demonstrate a constant direct relationship, although a rough parallelism was discernible, between the gastric secretory activity and the behavior for pH values of the contents of the second portion of the duodenum. Other observers (20, 21, 22, 26, 44, 45, 55), using men as subjects, have also remarked on the apparent lack of relationship between gastric and duodenal acidity.

The investigation to be reported was undertaken to supply some needed information concerning the acidity and the neutralizing ability of the contents of the first part of the duodenum in normal persons. The method of study employed was designed to surmount the shortcomings and meet the objections raised to previous work. The results, we hoped, would prove of physiologic interest and would afford better criteria of the acid factor in duodenal ulcer.

### MATERIAL

A subject was considered as "normal" if there was no evidence of fever or of any acute, chronic, infectious, metabolic or cachectic disease which might affect gastric secretion and if Roentgen-ray study showed no abnormality of the stomach and duodenum. Some of the individuals were examined additionally with the gastroscope, by cholecystography and by biliary drainage and these also yielded negative findings. Since most of the subjects were drawn from the Out-Patient Gastro-Intestinal Clinic of the Jefferson Hospital, it was not uncommon to encounter symptoms referable to the digestive system. If the above requirements for normalcy were met, however, the existence of functional complaints was not regarded as adequate reason to exclude an individual from this study. Likewise, since achlorhydria is an expected finding in a recognized percentage of "normal" persons (2, 4, 29, 34, 37, 56, 57, 65), lack of free acid in the stomach was not considered disqualifying.

Gastric secretion is a dynamic process which, even in "normal" individuals, displays not only daily fluctuation (1, 13, 62) and seasonal changes (63) but also varies with age (10, 11, 12, 65), sex (37, 56, 65), size, shape and position of the stomach (29), physical fitness (2, 11), physical build (64), occupation (58), character of the diet (58), environment (58), mental condition (58), use of tobacco (58) and with the presence and degree of any anemia (28, 37.) It is practically impossible to establish experimental con-

\*From the Departments of Medicine and Physiology of The Jefferson Medical College of Philadelphia.

†Aided by a Grant from John Wyeth & Bro., Inc.

‡Ross V. Patterson Fellow in Gastro-Enterology.

Portion of Thesis submitted by Dr. Berk to the Faculty of the Graduate School of Medicine of the University of Pennsylvania in partial fulfillment of the requirements for the Degree of Doctor of Medical Science (D.Sc. (Med.)) for graduate work in Internal medicine. Submitted February 6, 1942.

ditions or select a group of normal subjects which will assure standardization of all these variables. Therefore, we felt that our purposes would be sufficiently served by the random selection of individuals who merely met the qualifications for normalcy which we had imposed. Furthermore, our primary interest lay in observing the reaction and neutralizing ability in the duodenal bulb be the gastric secretion what it may; variations in gastric acidity were, in fact, desirable.

Of 23 subjects studied 21 were selected (14 males and 7 females) whose experiments were considered completely satisfactory with respect to technic. The age of the entire group ranged from 22 to 51 years with an average age of 35.5 years. The males ranged from 22 to 51 years of age with an average age of 32.5 years; the females from 29 to 49 years of age with an average age of 41.5 years.

### METHOD

Each subject was examined in the morning before breakfast and following a 12 hour fast. Through the use of a specially constructed double lumen tube and a method that permitted more or less fluoroscopic control as well as radiographic proof of the position of the tube (6), material was simultaneously aspirated from the pars pylorica and the duodenal bulb at 10 minute intervals. Specimens were collected for  $\frac{1}{2}$  hour in the fasting state and for 2 hours after the ingestion of an Ewald meal consisting of 2 pieces of dry toast or stale bread and 250 cc. of tap water.

The pH of each specimen was immediately determined by means of a Leeds-Northrup pH Indicator which uses a glass electrode. After filtration the free and total acidity of each specimen was estimated using Toepfer's reagent and phenolphthalein as the respective color indicators (7.) On each duodenal specimen, in addition, there was determined what was called the excess neutralizing ability (5, 7.) This consisted of the amount of N/10 hydrochloric acid necessary to lower the pH to the point at which Toepfer's reagent indicated a positive reaction for free acid (5.)

Out of 29 experiments 23 were accepted as being technically satisfactory. These involved 2225 separate determinations including 620 pH readings, 647 estimations of free acid, 641 estimations of total acidity, and 317 determinations of excess neutralizing ability of the duodenal contents. In expressing the results the four readings made in the fasting state were averaged to give a single fasting value.

### RESULTS

#### Acidity in pH Units (Fig. 1)

*Stomach.* As compared with the values reported by others in normal persons (15, 25, 35, 49, 50, 54), the average gastric acidity in pH units obtained in our subjects was less. No real comparison, however, can be made with previously reported pH values in humans because of the variation in circumstances and because of the inclusion in our group of some individuals with very low acid secretory levels. The gastric pH in normal humans differed in several respects from that in normal dogs fed the same meal (7), the most important difference being the lower pH values in dogs (49.)

*Duodenum.* There was a consistent difference in the pH of samples collected simultaneously from areas

just above and just below the pylorus. In the post-meal period the difference in the average values was approximately 2.25 pH units. This difference bespeaks a considerable neutralization in the course of passage through so short an anatomical stretch for it is to be remembered that an elevation of 1 pH unit represents a reduction in acidity of about 90%.

In the duodenum the average pH dropped no lower than 3.8. Not only was it not uncommon, however, for individual readings to drop below the critical value of pH 3.5 which we had adopted for free acid (5), but approximately 13 of all the duodenal postcibal samples (31.7%) had pH values of such magnitude. This percentage is almost twice as great as that found in dogs fed the same meal (16.4%). In view of the higher hydrogen ion concentration in the gastric contents of the dogs, it appears that duodenal neutralization is more effective in these animals than it is in man.

#### Free Acid (Fig. 2)

*Stomach.* The curve obtained by plotting the average values for gastric free acid was only roughly similar to that for the average gastric pH (Fig. 1); the most striking difference was in the period between 50 and 90 minutes after the meal during which time the average free acid showed a steady increase while the average pH remained practically unchanged. It is of even greater interest to note the divergence between the curves for average gastric free acid and average duodenal pH (Fig. 1.) The discrepancies between these indexes attest to the lack of correlation between the acidity simultaneously determined in the stomach and duodenal bulb.

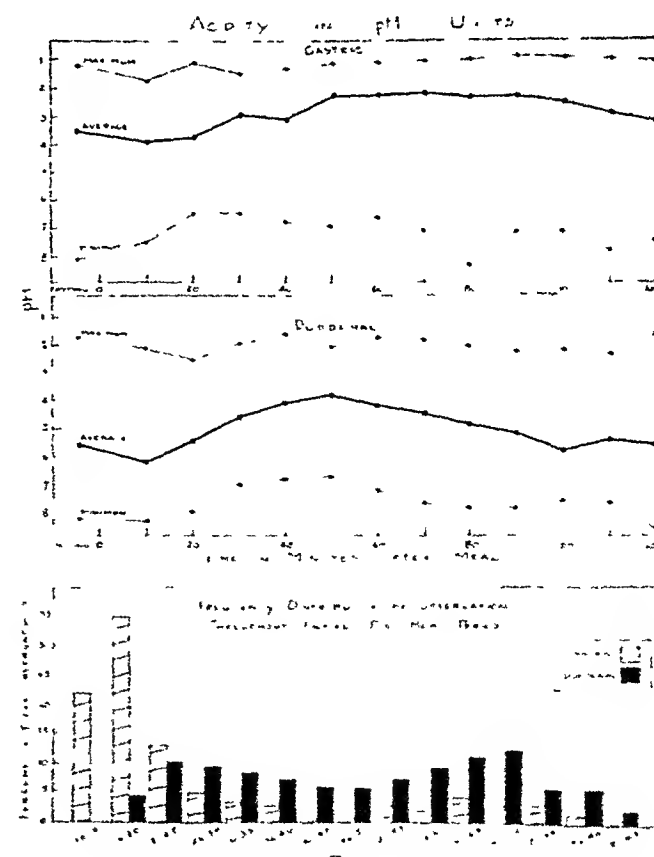


Fig. 1. Acidity in pH units of samples collected simultaneously from just above and just below the pylorus.

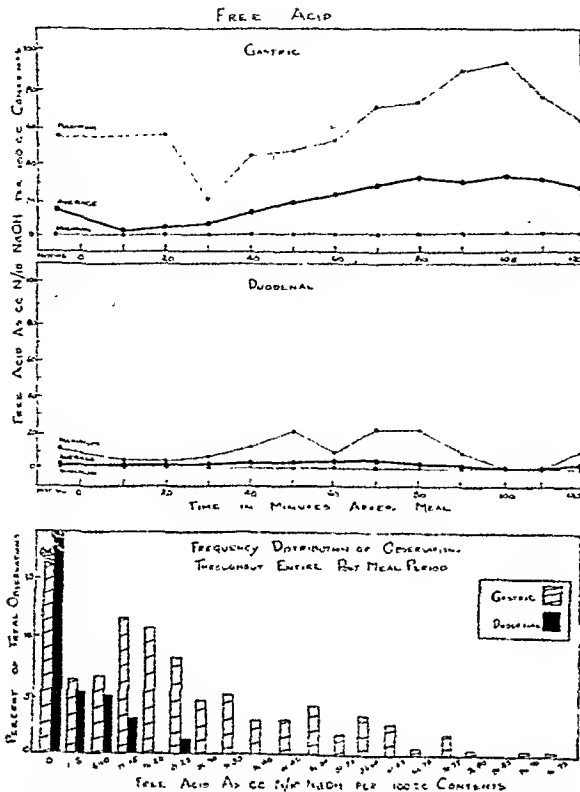


Fig. 2. Free acid as determined on samples collected simultaneously from just above and just below the pylorus. (No maximum value was plotted at the 10 minute interval because of the failure to secure a sample at this time from a subject whose values at the other intervals were consistently the highest ones obtained.)

**Duodenum.** From the standpoint of the average values, an absence of free acid in the contents of the first part of the duodenum appeared to be characteristic; still, 15.2% of all the post-meal specimens yielded a positive colorimetric reaction for free acid. With our technic the filtration and dilution of the samples preparatory to colorimetric titration introduces an error that results in some false negative readings (5.) Since our end point with Toepfer's reagent was in the neighborhood of pH 3.5 (5), it must be assumed that all specimens with a pH of 3.5 or less in the unfiltered and undiluted state contain free acid. Using such a criterion almost 1/3 (31.7%) of all the post-meal duodenal samples contained free acid. Colorimetrically 66.6% and electrometrically 75% of all the subjects showed free acid in their duodenal contents at some time during the post-meal phase. In 33.3% of the subjects colorimetrically and in 55% electrometrically free acid was present in 3 or more consecutive post-meal samples.

#### Total Acidity (Fig. 3)

**Stomach.** As was noted in the case of free acid, the gastric total acidity also displayed a lack of close parallelism with the pH in both the stomach and duodenum (Fig. 1.)

**Duodenum.** The line representing the plotted values for average duodenal total acidity adopted a pattern which simulated that in the stomach, yet it too was not closely parallel; in the interval from 60 to 100

minutes postprandial the former diverged from the latter and evidenced a completely opposite type of curve.

The foregoing observations may be taken as additional evidence of the absence of a constant relationship between the acidity determined at the same moment in the stomach and duodenal bulb.

As compared with normal dogs fed the same meal, normal humans had a distinctly lower total acidity in the stomach yet, in the duodenal bulb, the average total acidity was just about equal.

#### Excess Neutralizing Ability of the Duodenal Contents (Fig. 4)

We have previously defined excess neutralizing ability as a measure of the reserve capacity which the contents of the duodenal bulb possess to neutralize, buffer and dilute the chyme received from the stomach above that necessary to offset the free acid content (5, 7.)

During the first 50 minutes following the meal the excess neutralizing ability of the duodenal contents fell as the gastric and duodenal acidity rose. Thereafter, however, the excess neutralizing ability increased progressively despite a continued elevation of the gastric acidity; this probably accounts for the decrease in duodenal acidity observed during that period. The simultaneous increase in duodenal pH suggests, moreover, that the neutralizing mechanism was in the ascendancy.

Here again the neutralizing capacity of the contents of the duodenal bulb in man seems less than that in dogs. As compared with these animals the average excess neutralizing ability of the contents of the first

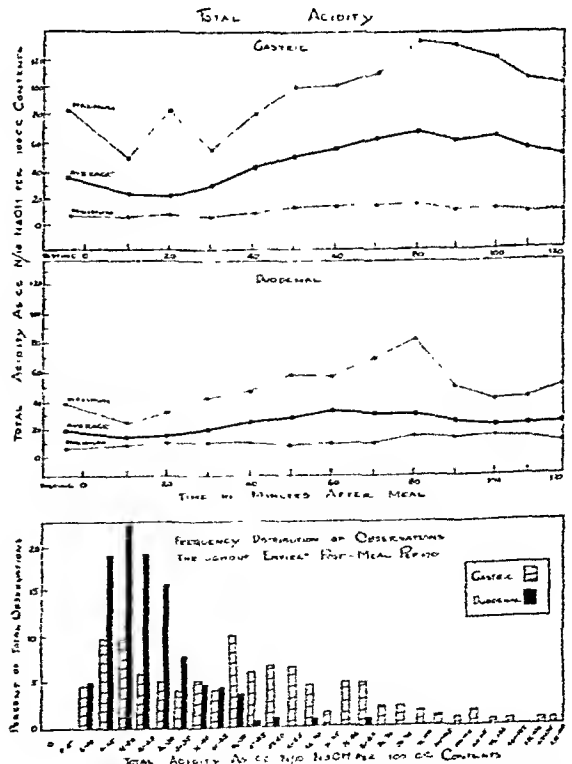


Fig. 3. Total acidity of samples collected simultaneously from just above and just below the pylorus.

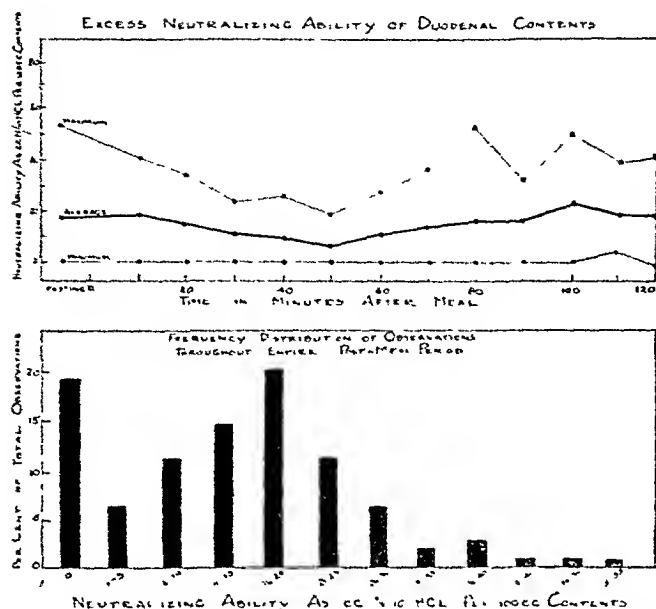


Fig. 4. Excess neutralizing ability of the contents of the first part of the duodenum.

part of the duodenum in man was less and the values in terms of clinical units were restricted to a narrower range (7.)

#### DISCUSSION

Before attempting any interpretation of the results, it should be made clear that there are recognized deficiencies in the method of study employed which permit a fair amount of experimental error (6.) Every effort was exerted to be certain of the source of the samples collected and many specimens of doubtful origin were discarded. Nevertheless, some of the specimens considered as emanating from the first part of the duodenum may have been drawn from some section of the pars pylorica or from the second part of the duodenum. By the same token, some of the specimens considered as pars pylorica in origin may have been taken from other adjacent parts of the stomach. To some extent these errors neutralize each

other, still the resultant average cannot be considered as thoroughly characteristic of the situation in the areas described. For this, as well as for other reasons, the figures obtained are not meant as standards for the acidity in the contents of the duodenal bulb of all normal persons.

Contrary to the belief held in many quarters, the duodenal bulb normally in man is an acid area. In the fasting state its contents have an average pH of about 5.6 and after an Ewald meal the average pH is about 5.0.

The contents of the first part of the duodenum in normal persons, as Morton (51) partially demonstrated, generally display a considerable capacity to neutralize, buffer and dilute the gastric chyme. Measured by its excess neutralizing ability, the contents of this area appear capable under most circumstances of handling more acid than that which is presented. In spite of this, almost 1/3 of all post-Ewald meal samples may be expected to contain free acid. In our group, moreover, about 3/4 of all the subjects showed free acid in their post-meal duodenal contents at some time and in about 1/2 of them free acid was present in 3 or more consecutive samples. The latter observations are contrary to those reported by Morton (51) and abnegate, at least insofar as the first part of the duodenum is concerned, the suggestion that the appearance of free acid in the duodenal contents be considered as of some diagnostic importance (19, 21, 22, 26, 51.)

Generally speaking, individuals with higher gastric acidities would be expected to have higher duodenal acidities (20, 23.) In normal people, however, increases in gastric acidity do not appear to be accompanied by increases in duodenal acidity of equal degree. Table I shows the differences in the average values for gastric and duodenal pH in the entire group of normal persons we studied (21 subjects) as compared with those members of this group who displayed free acid in their gastric contents at some time after the meal (19 subjects.) It will be seen that the differences in gastric pH between the group as a whole and

TABLE I

Comparison between the average gastric and duodenal pH of the entire group of normal persons (A) and those members of this group who showed gastric free acid at some time after an Ewald meal (B)

| Time in Minutes After Meal | Average Gastric pH (Units) |                       |            | Average Duodenal pH (Units) |                       |            |
|----------------------------|----------------------------|-----------------------|------------|-----------------------------|-----------------------|------------|
|                            | Entire Group (A)           | Gastric Free Acid (B) | Difference | Entire Group (A)            | Gastric Free Acid (B) | Difference |
| 10                         | 3.85                       | 3.66                  | -.20       | 6.32                        | 6.28                  | -.04       |
| 20                         | 3.60                       | 3.60                  | 0          | 5.58                        | 5.50                  | -.08       |
| 30                         | 2.89                       | 2.90                  | +.01       | 4.65                        | 4.53                  | -.12       |
| 40                         | 3.03                       | 2.58                  | -.45       | 4.10                        | 3.82                  | -.28       |
| 50                         | 2.29                       | 2.04                  | -.25       | 3.84                        | 3.56                  | -.28       |
| 60                         | 2.29                       | 1.82                  | -.47       | 4.15                        | 4.01                  | -.14       |
| 70                         | 2.28                       | 1.73                  | -.55       | 4.49                        | 4.16                  | -.33       |
| 80                         | 2.37                       | 1.68                  | -.69       | 4.75                        | 4.45                  | -.30       |
| 90                         | 2.33                       | 1.81                  | -.52       | 5.12                        | 5.00                  | -.12       |
| 100                        | 2.47                       | 2.22                  | -.25       | 5.59                        | 5.59                  | 0          |
| 110                        | 2.86                       | 2.55                  | -.31       | 5.31                        | 5.31                  | 0          |
| 120                        | 3.08                       | 2.83                  | -.25       | 5.43                        | 5.43                  | 0          |



the special achlorhydria-free group, are greater than the corresponding differences in duodenal pH between these same groups. Similarly, in presenting the results, attention was called to the lack of good correlation between the several indexes of gastric acidity and between these and the simultaneously determined duodenal acidity. The conclusion appears justified, therefore, that the customary observations of acidity in the stomach cannot be relied on with any certainty to indicate the behavior of the corresponding effective acidity in terms of pH in the duodenal bulb. Furthermore, the evidence obtained indicates that gastric acidity per se is but one of the factors concerned in the regulation of the reaction of the duodenal contents (20, 21, 33, 51, 60.)

It is a matter of some physiologic interest that normal people exhibit a neutralizing ability in the first part of the duodenum which is decidedly inferior to that of normal dogs. The latter animals are notoriously resistant to peptic ulceration and rarely, if ever, display a naturally occurring chronic duodenal ulcer. Inasmuch as the values for gastric acidity in the group of dogs studied were distinctly greater than the same values in the group of humans observed, there is some support for the thought that perhaps the factors that render man prone to develop chronic duodenal ulcer lie as much or more in deficient duodenal neutralization as in gastric hypersecretion (33, 51.)

### SUMMARY AND CONCLUSIONS

1. The important "ulcer-bearing" first part of the duodenum in normal persons is an acid area with an

average pH in the fasting state of about 5.6 and after an Ewald meal of about 5.0.

2. The duodenal bulb in normal subjects is endowed with a capacity to neutralize, buffer and dilute gastric chyme that generally exceeds the physiologic needs.

3. Free acid is usually but not constantly absent in the contents of the duodenal bulb in normal people; its presence cannot be construed as an abnormal finding.

4. The neutralizing ability of the contents of the first part of the duodenum is ineffective (pH 3.5 or less) in many normal subjects at some time or other after an Ewald meal. Usually, however, the extent to which the neutralizing ability is overcome is not great, and the duration of its ineffectiveness is short.

5. None of the customary measures of gastric acidity in normal persons can be used as a reliable index of the behavior of the corresponding effective acidity (pH) of the duodenal bulb contents.

6. The acidity of the gastric contents is not the only factor which determines the reaction of the contents of the first part of the duodenum.

7. The neutralizing power of the contents of the duodenal bulb in normal man is not as great as in normal dogs.

*Acknowledgement.* The authors wish to express their thanks to Dr. B. B. Vincent Lyon for his kind permission to use the patients and facilities of the Gastro-Intestinal Clinic and to Dr. Melvin Dillman and Dr. Karl Kornblum for their co-operation in performing the X-ray studies on each subject.

### REFERENCES

1. Alvarez, W. C.: Standards of Normal in Gastric Secretion. *Ann. Int. Med.*, 6:315, 1932.
2. Baird, M. Mc., Campbell, J. M. H. and Hern, J. R. B.: The Importance of Estimating Chlorides in the Fractional Test Meal Samples and Some Experiments with the Duodenal Tube. *Guy's Hosp. Rep.*, 74:23, 1924.
3. Baird, M. Mc., Campbell, J. M. H. and Hern, J. R. B.: Gastric Secretion, Physique and Physical Fitness. *Guy's Hosp. Rep.*, 74:339, 1924.
4. Bennett, T. I. and Ryle, J. A.: Studies in Gastric Secretion. V. A Study of the Normal Gastric Function Based on the Investigation of 100 Healthy Men by Means of the Fractional Method of Gastric Analysis. *Guy's Hosp. Rep.*, 71:286, 1921.
5. Berk, J. E., Thomas, J. E. and Rehfuess, M. E.: Limitations in the Use of Color Indicators in Gastric Analysis. *Am. J. Dig. Dis.* In press.
6. Berk, J. E., Rehfuess, M. E. and Thomas, J. E.: A Method for the Simultaneous Aspiration of the Contents of the Stomach and First Part of the Duodenum. *J. A. M. A.* In press.
7. Berk, J. E., Thomas, J. E. and Rehfuess, M. E.: The Reaction and Neutralizing Ability of the Contents of the Pyloric Antrum and First Part of the Duodenum in Normal Dogs Following an Ewald Meal. *Am. J. Physiol.* In press.
8. Berk, J. E., Thomas, J. E. and Rehfuess, M. E.: The Effect of Gastric Hypersecretion on the Reaction and Neutralizing Ability of the Contents of the First Part of the Duodenum in Normal Dogs. *Am. J. Dig. Dis.*, Sept., 1942.
9. Berk, J. E., Thomas, J. E. and Rehfuess, M. E.: The Effect of a Cream Meal on the Acidity and Neutralizing Ability of the Contents of the Duodenal Bulb in Normal Dogs. Unpublished data.
10. Bloomfield, A. L.: The Decrease of Gastric Secretion with Advancing Years: Further Observations. *J. Clin. Invest.*, 19:61, 1940.
11. Bloomfield, A. L. and Keefer, C. S.: Gastric Acidity: Relation to Various Factors Such as Age and Physical Fitness. *J. Clin. Invest.*, 5:285, 1928.
12. Bloomfield, A. L. and Keefer, C. S.: Gastric Motility and the Volume of Gastric Secretion in Man. *J. Clin. Invest.*, 5:295, 1928.
13. Boeckx, H. L., Bank, J. and Willard, J. H.: Achlorhydria with a Review of 210 Cases in Patients with Gastro-Intestinal Complaints. *Am. J. Med. Sci.*, 184:185, 1932.
14. Carnot, P., Koskowsky, W. and Libert, E.: Action de l'Histamine sur les sucs digestifs chez l'homme. *Compt. rend. soc. de biol.*, 86:670, 1922.
15. Christiansen, J.: (Cited by King, J. H. and Halpern, S. (35.)) (a) Däuber freie und gebundene Salzsäure im Mageninhalt I, II, III, IV. *Biochem. Ztschr.*, 46:24-93, 1912. (b) Einige Bemerkungen über die Mettsche Methode nebst Versuchen über aciditätsoptimum der Pepsinwirkung. *Biochem. Ztschr.*, 46:257, 1912.
16. Comfort, M. W.: Tests of Pancreatic Function. *J. A. M. A.*, 115:2044, 1940.
17. Comfort, M. W. and Osterberg, A. E.: Pancreatic Secretion in Man After Stimulation with Secretin and Acetylcholine. *Arch. Int. Med.*, 65:688, 1940.
18. Comfort, M. W. and Osterberg, A. E.: Pancreatic Secretion in Man After Administration of Different Stimulants: A Comparative Study. *Am. J. Dig. Dis.*, 8:337, 1941.
19. Einhorn, M.: Experiences with the Duodenal Contents. *J. A. M. A.*, 55:6, 1910.
20. Einhorn, M.: The Fractional Examination of the Duodenal Contents. *Am. J. Med. Sci.*, 156:317, 1918.
21. Einhorn, M.: Fractional Examination of the Duodenal Contents in Peptic Ulcer. *J. A. M. A.*, 77:1471, 1921.
22. Einhorn, M.: The Duodenal Tube and Its Possibilities. F. A. Davis Co., Philadelphia, 1926.
23. Einhorn, M. and Rosenbloom, J.: A Study of the Duodenal Contents in Man. *Arch. Int. Med.*, 6:566, 1910.
24. Evers, J. B.: Comparative pH Values Within the Stomach, Pylorus and Duodenum in Antacid Therapy. *Am. J. Dig. Dis.*, 7:431, 1940.
25. Fraenkel, P.: (Cited by King, J. H. and Halpern, S. (35.)) Die Wasserstoffionkonzentration des reinen Magensaftes und ihre Beziehungen zur elektrischen Leitfähigkeit und zur Titrimetrischen Acidität. *Ztschr. f. exper. Path. u. Therap.*, 1:431, 1905.
26. Friedenwald, J. and Sindler, J.: Fractional Analysis of the Duodenal Contents in Normal Individuals. *J. A. M. A.*, 77:1469, 1921.
27. Friedrich, L. V. and Barsony, T.: Untersuchungen mit der Gastro-Duodenalsonde. *Mün. med. Wchnschr.*, 72:519, 1925.
28. Fouts, P. J., Helmer, O. M. and Zerfas, L. G.: Gastro-Intestinal Studies. V. Gastric Juice in Anemias Other Than Pernicious Anemia. *Am. J. Dig. Dis.*, 1:677, 1935.
29. Gershon-Cohen, J., Shay, H. and Fels, S. S.: Experimental Studies on Gastric Physiology in Man. IV. The Relation of Size, Shape and Position of the Stomach to Its Acid Secretion. *Am. J. Roent.*, 40:695, 1938.
30. Gotschlich, E.: Die aktuelle Reaktion im Duodenum und oberen Dünndarm. *Deutsches Arch. f. klin. Med.*, 159:288, 1925.
31. Hume, H. V., Denis, W., Silverman, D. N. and Irwin, E. L.: Hydrogen Ion Concentration in the Human Duodenum. *J. Biol. Chem.*, 50:633, 1924.
32. Karr, W. G. and Abbott, W. O.: Intubation Studies of the Human Small Intestine. IV. Chemical Characteristics of the Intestinal Contents in the Fasting State and as Influenced by the Administration of Acids, of Alkalies and of Water. *J. Clin. Invest.*, 14:893, 1935.
33. Kearney, R. W., Comfort, M. W. and Osterberg, A. E.: Hydrogen Ion Concentration of the Duodenal Contents Under Fasting Conditions in Normal Persons and in Patients with Duodenal Ulcer: A Comparative Study. *J. Clin. Invest.*, 20:221, 1941.
34. Keefer, C. S. and Bloomfield, A. L.: The Significance of Gastric Acidity. *Bull. J. Hop. Hosp.*, 39:304, 1926.
35. King, J. H. and Halpern, S.: H-Ion Concentration Method of Gastric Analysis. *Trans. Am. Gastro-Enterol. Ass'n*, 1922.
36. Klumpp, T. G. and Neale, A. V.: The Gastric and Duodenal Contents of Normal Infants and Children. *Am. J. Dis. Child.*, 40:1215, 1930.

37. Lerman, J., Pierce, F. D. and Brogan, A. J.: Gastric Acidity in Normal Individuals. *J. Clin. Invest.*, 11:155, 1932.
38. Lim, R. K. S., Matheson, A. R. and Schlapp, W.:
  - (a) An Improved Method for Investigating the Secretory Function of the Stomach and Duodenum in the Human Subject. *J. Exper. Physiol.*, 13:333, 1922-23.
  - (b) New Gastro-Duodenal Technique. *Edinburgh M. J.*, 30:265, 1925.
39. Long, J. H. and Fenger, F.: On the Normal Reaction of the Intestinal Tract. *J. Am. Chem. Soc.*, 39:1278, 1917.
40. McClendon, J. F.: Acidity Curves in the Stomach and Duodenum of Adults and Infants, Plotted with the Aid of Improved Methods of Measuring Hydrogen Ion Concentration. *Am. J. Physiol.*, 38:191, 1915.
41. McClendon, J. F., Bissell, F. S., Lowe, E. R. and Meyer, P. F.: Hydrogen-Ion Concentration of the Contents of the Small Intestine. *J. A. M. A.*, 75:1638, 1920.
42. McClure, C. W.: Observations on the Physiology and Pathologic Physiology of External Pancreatic Functions. *Rev. Gastro-Enterol.*, 3:1, 1935.
43. McClure, C. W., Montague, C. W. and Campbell, L. L.:
  - (a) The Chemical Reaction of Duodenal Contents. *Boston M. and S. J.*, 190:237, 1924.
  - (b) The pH and Buffer Values of Duodenal Contents Derived from Normal Men. *Arch. Int. Med.*, 33:525, 1924.
  - (c) Studies on the Mechanism of External Pancreatic Secretion. *Boston M. and S. J.*, 192:527, 1925.
44. McClure, C. W. and Wetmore, A. S.: Studies in Pancreatic Function. Enzyme Concentration of Duodenal Contents After the Ingestion of Pure Foodstuffs and Food Mixtures by Normal Men. *Boston M. and S. J.*, 187:882, 1922.
45. McClure, C. W., Wetmore, A. S. and Reynolds, S.: Physical Characters and Enzymatic Activities of Duodenal Contents; Findings During Gastric Digestion in Normal Young Men. *J. A. M. A.*, 77:1468, 1921.
46. Martin, L.: Biliary, Pancreatic and Duodenal Studies. II. Estimation of Pancreatic Enzymes and Value of Such Determinations from a Clinical Standpoint. *Arch. Int. Med.*, 39:343, 1927.
47. Mettler, S. R.: The Reaction of the Human Duodenal Contents to Acid and Alkaline Meat Mixtures. *J. Clin. Invest.*, 8:561, 1930.
48. Meunier, L.: Du suc Gastro-Duodenal. *Presse Méd.*, 40:42, 1932.
49. Michaelis, L.: Some Problems Concerning the Gastric Juice. The Harvey Lectures. Series XXII, 59, 1927.

50. Michaelis, L. and Davidsohn, H.: (Cited by King, J. H. and Halpern, S. (35.)) Ueber Bedeutung und Messung der Magensaftacidität. *Ztschr. f. Exper. Path. u. Therap.*, 8:398, 1910.
51. Morton, C. B.: (a) Observations on Peptic Ulcer. VI. Preliminary Report of Clinical Experiments with Gastro-Duodenal Analysis. *Am. J. Med. Sci.*, 177:65, 1929; (b) Observations on Peptic Ulcer. *South. Surg.*, 3:316, 1934.
52. Müller, F.: Untersuchungen über den Duodenalinhalt beim Säugling. *Ztschr. f. Kinderh.*, 43:571, 1927.
53. Myers, F. J. and McClendon, J. F.: Note on the Hydrogen Ion Concentration of the Human Duodenum. *J. Biol. Chem.*, 11:187, 1920.
54. Norgaard, A.: Colorimetric pH Determinations of Test Meal Filtrates in Patients with Gastric Diseases and Their Relation to Titration Determinations. *Acta. Med. Scandinav.*, 60:498, 1924.
55. Okada, S. and Arai, M.: The Hydrogen Ion Concentration of the Intestinal Contents. *J. Biol. Chem.*, 51:135, 1922.
56. Pollard, W. S.: Histamine Test Meals. An Analysis of 988 Consecutive Tests. *Arch. Int. Med.*, 51:903, 1933.
57. Pollard, W. S. and Bloomfield, A. L.: Unexplained Gastric Acidity. *Arch. Int. Med.*, 48:412, 1931.
58. Rehfuess, M. E.: The Diagnosis and Treatment of Diseases of the Stomach. W. B. Saunders Co., Philadelphia, 1927.
59. Schiff, E., Eliasberg, H. and Mosse, K.: Zur Pathogenese der Ernährungsstörungen beim Säugling III. Mitteilung: Untersuchungen am Duodenalsaft. *Jahrb. f. Kinderh.*, 102:277, 1923.
60. Shay, H.: Unpublished data now in press. *Am. J. Dig. Dis.*
61. Silverman, D. N. and Denis, W.: Studies of the Pancreatic Enzymes in Fasting Duodenal Contents. *South. M. J.*, 17:549, 1924.
62. Vanzant, F. R. and Alvarez, W. C.: What is the Value of One Gastric Analysis? A Study of the Daily Variations in the Gastric Acidity of Two Normal Persons. *Proc. Staff Meet., Mayo Clinic*, 6:418, 1931.
63. Vanzant, F. R. and Alvarez, W. C.: Seasonal Variations in Gastric Acidity. *Proc. Staff Meet., Mayo Clinic*, 7:613, 1932.
64. Vanzant, F. R., Alvarez, W. C. and Berkson, J.: The Relation in Man Between Gastric Acidity and Height and Weight. *Am. J. Dig. Dis.*, 3:83, 1936.
65. Vanzant, F. R., Alvarez, W. C., Eusterman, G. B., Dunn, H. L. and Berkson, J.: The Normal Range of Gastric Acidity from Youth to Old Age. *Arch. Int. Med.*, 49:345, 1932.

## Some Observations on a Patient with an Ileostomy Bearing on the Diagnosis of "Irritable Colon"

By

EDWARD S. EMERY, JR., M.D.  
BOSTON, MASSACHUSETTS

THE following case is being reported because it suggests that in certain patients with a so-called "irritable colon" the source of the underlying disorder may reside in the small intestine.

H. N. was a young man of twenty-four years of age when he developed idiopathic ulcerative colitis. In spite of a careful medical regimen his disease progressed to such marked scarring that an ileostomy was performed in January, 1930. Following this, the patient made a gradual and satisfactory recovery. He is now in excellent health and living a normal existence in spite of the ileostomy.

For years before the onset of ulcerative colitis the patient had suffered from episodes which occurred every few weeks to a few months and would last from 24 to 48 hours. The attacks included both systemic and gastro-intestinal symptoms. The systemic symptoms consisted of malaise, lassitude and mild headaches. Accompanying these were intestinal symptoms of fulness, distention, cramps and at times some rumbling and gurgling, all of which were located in the lower abdomen. The location and general character of the symptoms were similar to those encountered in cases of "irritable colon."

Following the ileostomy the patient has continued to have these attacks as evidenced by the presence of

the same systemic symptoms. During these times the ileal discharges become very troublesome because of their frequency and the increase in their fluid content. He is kept busy changing his ileostomy bag and on these occasions the discharges become increasingly irritating. With the subsidence of his systemic symptoms the small intestine returns to its normal behavior. However, during this period of an overactive small intestine the patient no longer suffers from any distress such as distention or cramps.

In analyzing this story certain things appear to be pretty definite. It is apparent that the attacks which he had before the operation are similar to those which have occurred post-operatively because the systemic symptoms are the same. It seems evident that before the operation the colon was disturbed because the character and location of the abdominal symptoms were those which we physicians associate with an "irritable colon." Following the operation it became evident that the small intestine was also disturbed and there is no reason to doubt that a similar disturbance went on before the ileostomy. Since the abdominal symptoms have not recurred since the ileostomy, the operation must have influenced the behavior of the colon during these attacks. This could be due to the diversion away from the colon of the intestinal contents, or to an interference with the nerves supplying the colon. There is some evidence that the former

explanation is the correct one. That the so-called gastrocolic reflex continued to be active following the operation is shown by the fact that eating is accompanied or quickly followed by a desire to defecate and by rectal discharges. However, this evidence of colonic activity does not occur during the attacks. Therefore, it seems reasonable to believe that the colon was not primarily involved in an attack, but was secondarily stimulated by the abnormal discharges which in turn, depended upon a disturbance of the small intestine.

In summary we can say that this patient represents one of a group of individuals who suffer from functional periodic attacks popularly described as biliousness. His case demonstrates two important features. The first is that the small intestine rather than the colon is disturbed in this condition. The second feature of importance is that a disturbed small intestine may cause colonic symptoms without producing discomforts characteristic for the small intestine. This raises the question of whether the usual patient with an irritable colon" is in fact suffering from a disorder of the small intestine.

To most individuals a diagnosis of irritable colon suggests merely that the colon is reacting abnormally without much of any thought being given to the behavior of the other portions of the tract. In other words an irritable colon is unable to withstand the stress which is normally placed upon it. However, there is another possibility; namely, that the small intestine does its work so badly that it overwhelms a normal colon.

It is significant that the same foods which cause symptoms in patients with an "irritable colon" produce recognizable changes in the ileal contents of this patient. The coarser foods like cabbage increase the frequency and fluidity and, in general, have a shorter time of passage through the small intestine than finer ones. Freshly gathered vegetables such as green peas cause so many discharges that he has stopped eating them. However, peas which are two or three days old give no trouble.

Little attention has been accorded the small intestine in functional disorders, although Porges has emphasized the important role which this part of the tract may play. In the past, the reason for this neglect has been the lack of facilities for studying the jejunum and ileum. Now that the pioneer work of

Miller and Abbott with the multiple lumen tube and the improved roentgenological techniques have supplied new opportunities for studying this most important part of the tract, it seems probable that our understanding and classification of the functional disorders will change. Furthermore, it is to be hoped that a more intelligent and discriminating therapy will supplant our present rule of thumb procedures.

It has seemed to me worthwhile to report this case for the simple reason that although "functional indigestion" is a common ailment, very little is known about the mechanism of the gastro-intestinal disturbances which cause or accompany the symptoms. Thirty years ago when interest in gastric analyses served to attract attention to the stomach, this organ was blamed for most functional symptoms. Diagnoses of gastritis, hyperacidity, hypoacidity, etc., were common. During subsequent years the profession's interest centered more in the lower tract with the result that diagnoses implicating the colon became more frequent. Of all these terms, the one used by the late Dr. B. W. Sippy has met with the greatest favor and "irritable colon" is now a popular expression.

Until our knowledge of the functional patient improves, it would be desirable to eliminate the term "irritable colon." The trouble with the use of such a term is the implication to many minds that the colon is primarily involved; whereas, the case reported here demonstrates that this is not necessarily true. It is important not to mislead ourselves into possible false ideas by the use of indefinite terms. The use of "functional disorder" in place of "irritable colon" has the advantage of implying no more than we know about the nature of the disturbance.

#### SUMMARY

The case which has been reported had always suffered from periodic attacks associated with systemic and gastro-intestinal symptoms. Later, he developed a chronic ulcerative colitis for which an ileostomy was performed. Following the operation he did not experience gastro-intestinal symptoms with these attacks although he could recognize that the small intestine was misbehaving.

These observations suggest that the disturbance in some patients with a so-called "irritable colon" may reside in the small intestine.

## Segmental Spasms of the Esophagus and their Relation to Parkinsonism

By

ABRAHAM PENNER, M.D.

and

LEONARD J. DRUCKERMAN, M.D.\*

NEW YORK, NEW YORK

IT has been customary to divide esophageal diverticula into pulsion and traction varieties. In 1926, Gregoire (1) published the report of a case which fell into neither of these two categories. This concerned a 58 year old woman with a four year history

of increasing dysphagia. Radiographic examination showed a bulbous dilatation of the esophagus located at the level of the tortic arch. Exploratory thoracotomy revealed no evidence of organic disease and was followed by the eventual cure of the patient. Gregoire called this a false diverticulum of the esophagus.

In the same year Bársony (2) described two cases

\*From the Radiographic and Surgical Services of the Gouverneur Hospital, New York, N. Y.  
Submitted February 6, 1942.

of "functional esophageal diverticula," occurring in association with duodenal ulcer. In one there was a single bulbous dilatation of the esophagus; in the other there were three such dilatations separated by smooth bordered constrictions. He noted that the dilatations appeared only upon contraction of the esophagus in association with the act of deglutition. He considered them to be due to reflex relaxation of the esophagus, and therefore called them "relaxation diverticula." The following year, in association with Polgár (3), he described nine cases of which five presented multiple diverticula. These were associated with other disease of the esophagus or duodenum. Thus, in six of his cases a duodenal ulcer was also present, and in two, typical traction esophageal diverticula were noted. However, five of his patients did not present the typical radiographic appearance of functional diverticula but had genuine traction diverticula. The others had typical "functional diverticula." Subsequently, Bársony (4) elaborated upon his ideas as to the reflex nature of these diverticula, considering them to be a "secondary" disease in accordance with the concepts of Rössle (5.)

Since these first descriptions a small number of additional cases have been reported. In 1928, Teschen-dorf (6) described such a case and characterized the appearance of the esophagus as resembling a string of pearls. He obtained incomplete relief of the symptoms and partial disappearance of the diverticula for forty-five minutes, following the administration of 0.5 mg. of atropine. This same case was subsequently reported by Panhuysen (7), who indicated that the esophageal deformities had persisted unchanged for a period of fifteen months and that while the symptoms were less marked, the deformities remained.

Fleischner (8) observed a group of such cases and considered the diverticula the result of a fibrous, scarifying mediastinitis. In discussing Fleischner's paper, Reich (9) pointed out that in these cases the disease differed from typical functional diverticula. Thus, the latter occurred much less frequently and were more often accompanied by severe dysphagia. He pointed out that characteristically there were single or multiple contractions or spasms of the esophagus in its thoracic portion, accompanied by a marked motor unrest of this organ. Typical, also, was the sudden appearance of one or more diverticula whose size, form and contours might vary. Reich pointed out that at autopsy examination of the esophageal mucosa and musculature as well as the entire mediastinum revealed no disease. A typical case is described by Schinz, Baensch and Friedl (10) in their text book. They emphasize the fact that it is only in the rarest instance that the condition is influenced by atropin.

In 1931, Palugyay (11) described a condition which he entitled "Spastic, pseudo-diverticula of the Esophagus." He indicated their great rarity and described the changes as intermittent, circular, spastic constrictions occurring in the esophagus, usually at several levels at the same time. The constrictions were not complete and there appeared simultaneously above them a relaxation of the esophageal wall so that there developed an apparent ballooning-out between two such spasms. This was accompanied by marked motor unrest of the esophagus.

Two years later, Schatzki (12), in his monograph on the esophagus, described similar diverticula associ-

ated with single or multiple traction diverticula. He considered the multiple dilatations of the esophageal wall to be the result of a diminished contractility of the wall accompanied by local areas of weakness corresponding to the dilatations. Due to the radiographic morphology he coined the name "Kräuselung" (curling), for this condition. He pointed out that it was likely to occur in elderly persons.

Palugyay and Pések (13) in 1934 described a typical instance in a 61 year-old man. They observed that always the narrowings and dilatations appeared only a few seconds after the beginning of the act of swallowing. They disappeared with the cessation of the esophageal phase of deglutition, and recurred after the initiation of another act of swallowing. The writers noted that even swallowing without a bolus could cause the appearance of these changes. They

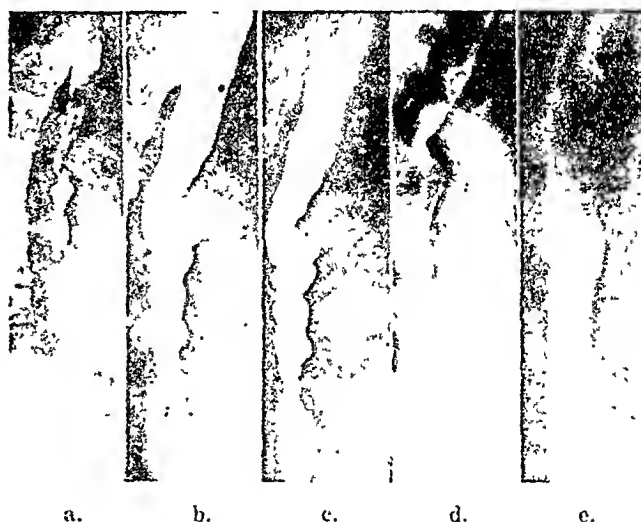


Fig. 1. Case 1. a. Shows the segmental contractions of the esophagus twelve days after the establishment of a gastrostomy for alimentation. b. Status about one month later showing the persistence of the segmentation as a response to the initiation of the esophageal phase of deglutition. c. Demonstrates the persistence of the spastic deformities 22 months after b. d. Taken one week after c. The patient had been taking gradually increasing doses of Rabellon in that interval. The spastic deformities are less marked, though still present. e. Three weeks later than c. During these three weeks Rabellon had been taken daily. The esophagus shows no evidence of the presence of pseudodiverticula.

considered the lesions due to an intrinsic defect of the esophageal wall.

In the past two years one of us (A. P.) has had the opportunity of observing four instances of this condition and has been able to study two of the patients.

Case 1. (No. 43687 L. M.) Fig. 1. An 80 year-old Italian woman was admitted to the Gouverneur Hospital on December 1, 1939, complaining of progressively increasing dysphagia and postprandial regurgitation, of six months' duration. During the week prior to admission she had been unable to swallow food or fluid except for an occasional teaspoonful of water. Fluoroscopy, elsewhere, had revealed an esophageal obstruction. In addition to the dysphagia, there had been a distinct change in her voice so that she was hoarse. A marked loss of weight had occurred. Her past history was non-contributory.

Examination revealed a thin, emaciated, dehydrated female, with marked evidence of generalized arteriosclerosis. Her blood pressure was 145/64. There were no ab-

dominant masses. Laryngoscopic examination was negative. Neurological and psychiatric examination revealed only a tremor of the hands and absence of the ankle jerks.

Laboratory Data: Hemoglobin 70%. White blood count 7,500. Differential count: Polynuclear leucocytes 76%; lymphocytes 31% and transitional cells 3%. The blood non protein nitrogen was 32 mg. %. The Kline test was negative. The urine specific gravity was 1.022. It showed a trace of albumen but no sugar.

She was given parenteral fluids containing glucose and salt until the dehydration was relieved. Since deglutition did not improve during the two days in which this was done, it was decided to perform a gastrostomy for feeding purposes. Accordingly, under local anesthesia a typical Kader-Senn gastrostomy was performed. Twelve days post-operatively, fluoroscopic and radiographic examination of the esophagus showed the typical multiple sacular dilatations of the esophagus, characteristic of pseudodiverticulosis of this organ. There were noted marked spastic, intermittent segmentations of the esophagus, accompanied by a delay, but no real obstruction to the flow of barium through the cardia. Identical findings were observed on January 11, 1940. Esophagoscopy, performed shortly before discharge from the hospital did not reveal any neoplasm, obstruction or diverticula and the esophagoscope entered the stomach readily. Two and one-half weeks post-operatively she was able to swallow small amounts of fluid, but not enough to keep her from losing weight. It was only six weeks after operation that sufficient amounts of food could be taken orally to permit discontinuance of the gastrostomy feedings and removal of the gastrostomy tube. She was discharged on January 26, 1940, with the wound well healed. During the subsequent nine months she was able to maintain her weight. However, there was always a varying degree of dysphagia present, which on several occasions became intense enough to result in vomiting. She was again X-rayed on October 7, 1941, at which time we had an opportunity of more clearly observing the features of the esophageal lesion.

It was noted that the barium meal, instead of immediately descending to the level of the cardia, following the act of swallowing, would be delayed at the level of the arch of the aorta. This delay was caused by the simultaneous appearance in the middle two-thirds of the thoracic esophagus of multiple constrictions. These developed suddenly, about one second after the mouthful of barium was transferred to the pharynx, and was followed in a few seconds by a simultaneous relaxation of the entire esophageal wall. At no time was the usual peristaltic wave seen in the esophagus. Aside from this delay, there was no obstruction to the entrance of the opaque meal into the stomach.

At the time of this observation, the patient presented a typical pill-rolling tremor of the hands as well as a tremor of the tongue and lower lip.

She was given tablets containing a combination of the alkaloids of the belladonna root (hyoscyamine, atropine and scopolamine)\* in gradually increasing doses for the next seven days, and again observed by fluoroscopy and X-ray. At this time, the segmentation of the esophagus, while still present, was nevertheless, neither as intense nor were the segmentations as numerous. She spontaneously volunteered that her dysphagia was less marked. The medication was increased in dose to two tablets three times daily. On October 28, 1941, fluoroscopic examination of the esophagus failed to reveal any evidence of spasm, constriction or irritability. In addition, the tremor of her tongue and lower lip had disappeared, while the pill rolling had markedly diminished. When questioned she stated that she had not been troubled with dysphagia during the week past.

\*Alkaloids of U.S.P. belladonna combined in tablet form, each tablet contained hyoscyamine 0.4507 mg., atropine sulphate 0.0372 mg. and scopolamine hydrobromide 0.0119 mg., marketed under the trade name "Rabellon" by Sharp & Dohme.

Case 2. (No. 2661, P. McG.) Fig. 2. A 65 year-old white male was admitted with a six month history of knifelike epigastric and periumbilical pain, coming on five to ten minutes after meals. The pain radiated along the left costal margin. His appetite had decreased and he had lost sixty pounds in weight. On examination there was a suggestion of a mass under the left costal margin, as well as edema of both lower extremities. The patient presented a mask like facies. There was a distinct tremor of the tongue, lower lip and fingers. This was present at rest and was neither accentuated nor relieved by voluntary motion.

Laboratory Data: Blood pressure 175/75. Hemoglobin 48%. Red blood count 3,360,000. White blood count 7,200. Differential count: Polynuclear leucocytes 65%, lymphocytes 35%. Kahn negative; Urine: Specific gravity 1.022. There was no albumin or sugar.

Six days after admission, fluoroscopy and radiography



Fig. 2, Case 2. a. Shows the typical appearance of the esophagus in spastic pseudodiverticulosis. b. Demonstrates the marked diminution of the intensity of the spasm after the administration of increasing doses of Rabellon for two weeks. At this time the Rabellon was stopped with the result that the spastic pseudodiverticulosis reappeared as in a. c. Complete disappearance of the deformities after therapy had been reinstituted for ten days.

revealed the presence of a large carcinoma involving the antrum and body of the stomach. In addition, typical multiple segmentations of the esophagus were observed, in every way corresponding to those described in our first case. Re-examination three days later after complete atropinization, confirmed these observations. Since the gastric carcinoma was apparently inoperable, it was decided to attempt to treat the esophageal lesion. He was accordingly started on a regimen of gradually increasing doses of the belladonna alkaloids. Two weeks later, re-examination showed an almost complete disappearance of the segmentation. The drug was then discontinued for ten days, whereupon the segmentations reappeared in their previous form. Reinstitution of therapy for ten days again caused the complete disappearance of the segmentations. Exploratory laparotomy at this time revealed an inoperable, diffusely infiltrating carcinoma of the stomach.



These two cases, as well as two others, which we observed only once, all presented the association of an apparently spastic type of disturbance in the esophagus with somatic manifestations of Parkinsonism. It was for this reason that the belladonna alkaloids were administered, in the hope that there might be subjective and objective improvement in the esophageal manifestations.

It is well known that the proximal portion of the esophagus contains a large proportion of striated muscle in its circular muscle layer. In fact, Arey and Tremaine (14) in a careful study of seventy-four human esophaguses, with special reference to this point, found that in one instance the striated muscle extended practically to the cardia.

A study of the physiologic characteristics of the striated muscle of the esophagus demonstrates that its response to stimuli are the same as those of somatic striated muscle. Strickland-Goodall (15) as well as Waller (16) and others (17) have shown that this response consists of very rapid, tetanic-like twitch with a very rapid rise and fall in tension, in contrast to the smooth muscle of the lower end of the esophagus which responds with a slow rise after a long latent period, followed by a long relaxation phase. Likewise, in contrast to smooth muscle, the striated muscle of the esophagus is paralyzed by curare (Langley (18).)

The striated muscle of the esophagus is supplied from a separate motor nucleus, the Nucleus Ambiguus, located in the medulla. Its axones join those of the dorsal motor nucleus of the vagus and form part of the vagal trunk, distributed to the esophagus. (Onuf and Collins (19), Molhant (20), Malone (21), Ariens-Kappers (22).) Stimulation of a vagal trunk results in a spastic contraction of the entire esophagus (Kahn (23), Inoaka (24).) However, stimulation of one of the smaller branches, before its entrance into the esophagus, does not result in the starting of a peristaltic wave but in the appearance of a segmentally localized spasm, which does not spread to the neighboring muscle areas. Furthermore, it is impossible to set up a peristaltic wave in the esophagus by stimulating the motor branches of the vagus to this organ. (Inoaka.)

Mosso (25) was the first to demonstrate that the esophageal phase of deglutition was a highly complex series of coordinated reflexes dependent upon a central coordinating nucleus. In this he was confirmed by Kroenecker and Meltzer (26), and others (27.) They showed that if this phase of deglutition was initiated by stimulation of the superior laryngeal nerve, it would extend down the entire length of the esophagus even if a segment of the latter were removed, provided that the extrinsic vagal nerve supply was intact.

V. Brück and Satake (28) in studying the action current in the esophagus, caused by the reflex deglutition resulting from stimulation of the superior laryngeal nerve, were able to demonstrate that the peristaltic wave of the esophagus, at least in so far as it passes over the portion of the esophagus supplied by striated muscle, does not correspond to a single wave of stimulation but to an advancing, tetanic contraction. A characteristic feature of the reflex phenomena involving striated muscle is a refractory period whose cause lies within the central nervous system (29.) This is true of the refractory period of the deglutition reflex in the striated muscular portion

of the esophagus (30.) In this respect it also differs from the smooth muscle in the intestinal tract in which Magnus (31) has shown that the refractory phase is referable to the local nerve plexus (Auerbach's) lying in the intestinal wall. Just as does striated muscle involved in other reflex movements, the striated muscular portion of the esophagus also possesses a supernormal phase. In this, following the refractory period, there is an interval during which deglutition is more readily elicited by afferent stimulation than before. This is also centrally conditioned. (Isayama (32), Reisch (33), Zwardemaker (30).)

It has been pointed out by Sherrington (29) that the reflexes of which the refractory phase constitutes a prominent feature are those concerned with cyclic actions occurring in rhythmic series, and included in this, the reflexes involved in deglutition.

Meltzer (27) demonstrated that the orderly progress of peristalsis in the esophagus is exclusively of central origin. This signifies that the first afferent impulse conveyed to the center of deglutition from the periphery, follows a path within the center, through several groups of ganglia. It thus causes the successive stimulation by efferent impulses, of the various muscles which accomplish the act of swallowing as well as of the several divisions of the esophagus, and causes their successive contraction.

It is obvious that an act of such complexity as deglutition would be susceptible to a wide variety of abnormalities as a result of injury to any one of the many central and peripheral nervous pathways. Its involvement in bulbar palsy, along with involvement of the larynx, is well known. The same is true of its involvement in pseudo-bulbar paralysis. In the latter there is not infrequently a dissociation in the simultaneous involvement of the other organs innervated from the medulla oblongata. Destruction of the supranuclear pyramidal tracts may involve any one of any group of such organs (Peritz (34), Thurel (35).) In such cases where deglutition is interfered with, it has usually been considered to be due to a paralysis of the constrictor muscles of the pharynx. In these cases the pyramidal tract is the supranuclear tract involved.

It has been known for many years that patients presenting the Parkinson syndrome may have difficulty in deglutition. We have been unable to find any reports of X-ray studies of the esophagus in such cases. Just as in the cases with pseudobulbar palsy of pyramidal origin, these cases may show a striking dissociation in the degree of involvement of the structures supplied by the motor nuclei of the medulla oblongata. Thus Kenzinger (36) has reported a case of typical Parkinsonism in which there was a marked tremor of the tongue and soft palate and in addition, a distinct tremor of the true vocal cords which were constantly performing alternating adduction and abduction movements. Similar observations have been made by Collet (37) in a case of post encephalitic Parkinsonism, in which difficulty in deglutition finally supervened. As Thurel has shown, the Parkinson type of pseudobulbar palsy presents symptomatology similar to that seen in the usual pseudobulbar paralysis and the same functions are affected, with the difference that in the former type it is not the hypertonia or paralysis of the muscle groups which causes the symptoms but the incoordination of the involuntary reflex muscular



movements. Ariëns-Kappers (22) has pointed out that, in addition to short inter-nuclear connections from nearby medullary centers, the Nucleus Ambiguus receives afferent fibers from several higher centers in the nervous system. Chief among these he notes the cortico-bulbar and cortico-striate fibers. The latter have been studied in great detail by Morgan (38) who was able to show that the Nucleus Ambiguus receives afferent fibers from the globus pallidus. In cats with experimental lesions placed in the latter location, he observed a distinct inability to perform the movements involved in deglutition. Unfortunately, the esophageal phase was not studied in these animals.

As we have stated above, one of us (A. P.) was struck by the clinical association of Parkinsonism with a dysphagia caused by a segmentally located spasm in that portion of the esophagus whose wall usually contains a great deal of striated muscle. We felt that the motor disturbance in the esophagus might be due to a lesion in the nervous pathways which served as a co-ordinating mechanism to control the sequence in which impulses are discharged by the motor nuclei involved in deglutition.

Jakob (39) has pointed out that the globus pallidum functions to co-ordinate movements caused by voluntary impulses reaching it by the cortex via the thalamus, and also co-operates in the performance of successive movements. Its destruction leads to a "deficit" in co-ordinate movements as well as in succession movements. He also points out that the entire act of deglutition is significantly affected in extrapyramidal disease and that the basal ganglia contribute to the central regulation of this act.

It was on this basis that therapy with Rabellon was attempted. We feel that the disappearance of the esophageal changes resulting from the use of this

drug lends further support to the idea that the latter represents an esophageal disturbance secondary to striatal disease.

On this basis it is possible to separate out from the heterogeneous group of pseudo-diverticula of the esophagus at least one category in which the mechanism is clear.

## SUMMARY AND CONCLUSION

The literature relative to spastic pseudodiverticulosis of the esophagus (functional esophageal diverticula, Krafäselung of the esophagus) has been reviewed.

Two typical cases are described. One patient entered the hospital because of symptoms of complete esophageal obstruction, so severe that a gastrostomy had to be performed for alimentation. This patient was watched for twenty-two months and continued to exhibit radiologically typical spastic segmentation of the esophagus.

Both cases occurred in aged individuals who exhibited evidences of Parkinsonism.

Administration of belladonna alkaloids, caused in both cases, complete disappearance of the spasms, and marked amelioration in the case which presented esophageal symptoms.

The clinical association of Parkinsonism with the syndrome of spastic pseudodiverticulosis of the esophagus in which changes observed radiographically are located in that portion of the esophagus containing striated muscle, correlated with the subjective and objective improvement obtained with belladonna alkaloids, and the recurrence seen upon stoppage of the treatment lend support to the suggestion that the so-called spastic pseudodiverticulosis of the esophagus is one of the manifestations of Parkinsonism.

## REFERENCES

- Grégoire, R.: Faux diverticule de l'oesophage cervicale. *Arch. des mal. App. digest.*, 16:251, 1926.
- Bárony, T.: Funktionelle Speiseröhrendivertikel (Relaxiondivertikel). *Wien. Klin. Wochr.*, 39:1363, 1926.
- Bárony, T. and Polgár, F.: Symptomlose, "funktionelle" Speiseröhrendivertikel. *Fortschr. Röntgenstr.*, 36:593, 1927.
- Bárony, T.: Das Divertikel als zweite Krankheit. *Wien. Klin. Wochr.*, 412:1308, 1928.
- Rösle, R.: Das runde Geschwür des Magens und Zwölffingerdarmes als zweite Krankheit. *Mitt. a.d. Grenzgeb. d. Med. u. Chir.*, 25:166, 1912.
- Teschendorf, W.: Die Röntgenuntersuchung des Speiseröhre. *Erg. med. Strahlenforsch.*, 3:174, 1928.
- Panhuyzen, A.: Über funktionelle Ösophagusdivertikel. *Röntgenpraxis*, 1:324, 1929.
- Fleischner, F.: Schwierige Mediastinitis und röntgenologisch erkennbare Veränderungen am Ösophagus. *Fortschr. d. Röntgenstr.*, 37:406, 1925.
- Reich, L.: Discussion of Fleischner, F. *ibid.*
- Schinz, H. R., Baensch, W. and Friedl, E.: Lehrbuch des Röntgendiagnostik. 3. Aufl. Leipzig, G. Thieme, p. 1612, 1931.
- Palugay, J.: Handbuch d. Röntgenkunde. Bd. 3. J. Springer, Vienna, pp. 112-113, 1931.
- Schatzki, R.: Reliefstudien an der normalen und krankhaft veränderten Ösophagus. *Acta Radiologica*, Supp. XVIII, 1933.
- Palugay, J.: Ablauf der Ösophagusperistaltik. *Röntgenpraxis*, 6:417, 1934.
- Arey, L. B. and Tremaine, M. J.: The Muscle Content of the Lower Esophagus of Man. *Anat. Rec.*, 56:315, 1933.
- Strickland-Goodall, J.: The Contraction of the Isolated Oesophagus. *J. Physiol.*, 33, Proc. i, 1905-06.
- Waller, A. D.: Utilization of the Oesophageal Muscles of the Cat for Purposes of Class Demonstration. *J. Physiol.*, 32, Proc. xxxd, 1905.
- Inoaka, T.: Weitere Studien zur Physiologie des Oesophagus, insbesondere zur funktionellen Differenzierung seiner quergestreiften und glatten Muskulatur. *Arch. für d. gesamt. Physiol.*, 204:368, 1924.
- McSwiney, B. A. and Robson, J. M.: The Response of Smooth Muscle to Stimulation of the Vagus Nerve. *J. Physiol.*, 68:124, 1929.
- Brücke, E. T. and Inouye, T.: Die Aktionsströme der Muskulatur des Kaninchensöesophagus bei Reizung des Nervus Vagus mit Einzelreizen. *Arch. für d. gesamt. Physiol.*, 145:162, 1912.
- Langley, J. N.: On Inhibitory Fibers in the Vagus for the End of the Oesophagus and the Stomach. *J. Physiol.*, 23:407, 1898.
- Onuf, B. and Collins, J.: Experimental Researches on the Localization of the Sympathetic Nerve in the Spinal Cord and the Brain. *J. Nervous and Mental Dis.*, 25:661, 1898.
- Molhant, M.: Le Nerf Vague-Etude Anatomique et Experimentale. *Le Névrose*, 11:137, 1910.
- Malone, E. F.: The Nucleus Cardiacus Vagi and Three Distinct Types of Nerve Cells which Innervate Three Different Types of Muscles. *Am. J. Anat.*, 15:121, 1913.
- Ariëns-Kappers, C. U.: Huber, G. C. and Crosby, E. C.: The Comparative Anatomy of the Nervous System of Vertebrates. Including Man. New York, The Macmillan Co., Vol. 1, p. 591, 1936.
- Kahn, R. H.: Studien über den Schluckreflex, II. Die motorische Innervation der Speiseröhre. *Arch. f. Physiol.*, 355, 1906.
- Inoaka, T.: Studien über die Innervation und Peristaltik des Ösophagus beim Säuger. *Arch. für d. gesamt. Physiol.*, 203:319, 1924.
- Mosso, A.: Ueber die Bewegung der Speiseröhre. *Untersuchungen zur Naturlehre von Moleschott*, 11:327, 1876.
- Kronecker, H. and Meltzer, S.: Der Schluckmechanismus, seine Erregung und seine Hemmung. *Arch. f. Physiol.*, supp. 329, 1883.
- Meltzer, S. J.: Ein Beitrag zur Kenntnis der Reflexvorkänge welche den Ablauf der Peristaltik des Ösophagus Kontrollieren. *Zentralbl. f. Physiol.*, 19:993, 1906.
- Meltzer, S. J.: On the Causes of the Orderly Progress of the Peristaltic Movements in the Oesophagus. *Am. J. Physiol.*, 2:270, 1899.
- Markwald, M.: Ueber die Ausbreitung der Erregung und Hemmung vom Schluckcentrum auf das Atemcentrum. *Zeitschr. f. Biol.*, 25:1, 1889.
- v. Brücke, E. T. and Satake, J.: Über die Aktionsströme des Kaninchensöesophagus während des Ablaufes einer Schluckwelle. *Arch. für d. gesamt. Physiol.*, 150:208, 1913.
- Sherrington, C. S.: The Integrative Action of the Nervous System. New Haven, Yale Univ. Press, 1911.
- Zwaardemaker, H.: Sur une phase Refractaire du Reflexe de Déglutition. *Arch. internat. de physiol.*, 1:1, 1904.
- Magnus, R.: Versuche am überlebenden Dünndarm von Säugern. *Arch. für d. gesamt. Physiol.*, 102:349, 1904.
- Isayama, S.: Nachweis einer übernormalen Phase des Schluckzentrums. *Zeitschr. f. Biol.*, 82:339, 1925.
- Reisel, O.: Zur Kenntnis der übernormalen Phase des Schluckzentrums nach Ablauf einer Schluckwelle. *Zentralbl. f. Biol.*, 83:557, 1925.

34. Peritz, G.: Pseudobulbär- und Bulbärparalysen des Kindesalters. Berlin, Karger, 1902.
35. Thurel, R.: Les Pseudo-Bulbaires. *Thèse de Paris*, 1929.
36. Kenzinger, J.: Sur Certains Aspects du Syndrome Pseudo-Bulbaire. *Thèse de Paris*, 1926.
37. Collet, F. J.: Troubles pharyngo-larynges dans un cas de park-

insonisme post-encephalitique. *Le J. de Med. d. Lyon.*, 12:429, 1931.

38. Morgan, L. O.: The Corpus Striatum. *Arch. of Neur. and Psychiat.*, 18:495, 1927.
39. Jakob, A.: Die Extrapyramidalen Erkrankungen. *Monographien aus d. Gesamtgeb. d. Neurol. u. Psychiat.*, 37:1, 1923.

## Redundant Gastric Mucosa Simulating Carcinoma of the Stomach

By

HERMAN J. MOERSCH, M.D.

and

JAMES F. WEIR, M.D.\*

ROCHESTER, MINNESOTA

**L**ITTLE mention of prolapse of the gastric mucosa and the necessity of distinguishing it from carcinoma of the stomach is made in the literature on gastroscopy. Roentgenologists have long been aware of this condition. Pendergrass, especially, has written extensively on the subject. Kantor described the condition under the heading of "giant rugae," and emphasized the fact that it may closely mimic carcinoma of the stomach roentgenographically. Konjetzny, Brunn and Pearl, Moutier, Schindler and others have called attention to the frequency with which gastritis may simulate carcinoma of the stomach. The difficulty in diagnosis becomes infinitely greater when such a type of gastritis is limited to a portion of prolapsed gastric mucosa; it will then test the diagnostic acumen of the gastroscopist to the utmost.

Prolapse of the gastric mucosa is relatively uncommon. The factors leading to its development are not definitely known. Eliason and associates were of the opinion that it might develop as the result of chronic irritation to the gastric mucosa. Pendergrass believed that it might arise from anything that would lead to the development of gastritis. It has been suggested that it is more likely to occur among people who eat great quantities of food, with resulting overstretching of the stomach and the subsequent formation of huge folds of mucosa. This latter hypothesis is not supported in all cases, however, because the patient with whom we are concerned herein had never been a heavy eater. We are inclined to believe that prolapse of the gastric mucosa is a manifestation of a developmental anomaly for similar alterations are encountered elsewhere in the gastro-intestinal tract. Furthermore, we believe that the gastritis which occurs in association with the prolapsed mucosa is a secondary process.

Prolapse of the gastric mucosa does not give rise to any characteristic clinical syndrome. Should the prolapsed gastric mucosa involve the antrum of the stomach (the site most frequently involved) and attain sufficient size and a long enough pedicle, it might conceivably give rise to obstructive symptoms. When the prolapsed mucosa is located in the body or in the cardinal end of the stomach, such a sequence of events is not likely to obtain. If the prolapsed mucosa is involved with gastritis it is possible that anemia might develop, because of the fact that the crest of the prolapsed portion of mucosa is more subject to irritation

than is normal mucosa, and may undergo ulceration, with subsequent bleeding.

Because of the rarity of prolapse of the gastric mucosa and the lack of reference to it in gastroscopic literature, we wish to report a case of this type. It is especially of interest because the true nature of the lesion was not recognized at gastroscopic examination. It is hoped that by our calling attention to this condition, others may avoid a similar error. The roentgenologist, with all due credit, did recognize the correct nature of the lesion, as was proved at the time of operation. Much is to be learned from the roentgenologists by virtue of their past experience with the condition.

### REPORT OF A CASE

The patient, a man sixty years of age, presented himself at the Mayo Clinic in January, 1938, complaining of extreme weakness. He stated that during the five preceding years he had noted dyspnea on exertion and had been subject to episodes of substernal pain which would extend down into both arms. The pain occurred only at night and was never precipitated by exertion. Four weeks before coming to the clinic he had had a light attack of influenza and since then had suffered from extreme exhaustion. In addition, he had noted a blotchy appearance of the skin.

On physical examination, the patient was found to be a tall, thin man who appeared older than his stated years. He seemed somewhat depressed. He weighed 170 pounds (77 kg.), which he stated was his normal weight. His face, chest and arms were covered with macular lesions. On palpation of the abdomen a sensation of resistance high in the epigastrium was manifested which suggested the possibility of an underlying mass. Otherwise, results of the physical examination were essentially negative. The eutaneous lesions proved to be those of eutaneomacular syphilis, a condition he had but recently contracted and for which he had recently received treatment at home. Reactions to flocculation tests of the blood were strongly positive for syphilis.

Special cardiology and electrocardiographic studies were carried out because of the history of substernal pain, but these failed to reveal any evidence of a cardiac disturbance. Results of the rest of the laboratory tests, including urinalysis, hematologic studies, studies of blood urea, sedimentation rate, and examination of the stools, were all negative or within normal limits. Roentgenologic examination of the thorax, spinal column, head and colon likewise failed to disclose anything abnormal.

Gastric analysis revealed no free hydrochloric acid, and in the gastric contents were considerable traces of blood. Roentgenologic examination of the stomach revealed a lesion, polypoid in character, on the posterior wall of the

\*Division of Medicine, Mayo Clinic  
Submitted February 27, 1942.



Fig. 1. Roentgenographic appearance of the gastric lesion.

stomach near the greater curvature (Fig. 1.) The roentgenologist thought the lesion most likely was submucous in character, and requested that the patient be returned for reexamination. Roentgenologic examination was repeated two days later, and at that time the roentgenologist reported marked hypertrophy of the gastric mucosa in the middle third portion of the stomach, on the posterior wall near the greater curvature. He felt that the condition probably was hypertrophic gastritis, but could not definitely rule out a malignant process. Gastroscopic examination was requested by the roentgenologist.

On gastroscopic examination, a large tumor mass was found projecting into the lumen of the stomach from the posterior wall near the middle third part of the stomach. The mucosa covering the tumor was nodular, and there was evidence of ulceration. The mucosa covering the rest of the stomach was atrophic, and vessels were easily discernible underlying the mucosa. An attempt was made to determine the pliability of the tumor-like mass by over-distending the stomach with air, but this had no effect on the nature of the tumor mass. The gastroscopic picture was not characteristic of carcinoma. The possibility that the lesion might be due to syphilis was considered, but, again, the usual gastroscopic picture characteristic of syphilis was not seen. It was finally concluded that the lesion most probably was carcinoma, although syphilis could not be definitely excluded.

Because of the gastroscopic observations the patient again was examined roentgenoscopically. At this examination the roentgenologist reported that the lesion definitely was not carcinoma, but that it was hypertrophy of the gastric mucosa.

The bizarre nature of the patient's condition, the uncertainty of the gastroscopic observations, the absence of free hydrochloric acid and the presence of blood in the gastric contents, in association with the presence of a questionable mass in the epigastrium, all seemed to indicate the advisability of surgical exploration of the

stomach. The patient himself was desirous of establishing definitely the exact nature of the gastric lesion.

Surgical exploration was carried out through a left rectus incision. On exploration of the stomach marked thickening of the walls of the stomach along the greater curvature, involving both the anterior and posterior walls of the lower two-thirds of the stomach, was found. Thickening was most marked along the greater curvature, but did not feel firm enough to be a neoplasm and did not feel like a polyp; rather, it imparted the sensation to the touch of a simple, inflammatory thickening. It was deemed advisable to resect the lower two-thirds of the stomach. The patient withstood the operation well, and recovered rapidly and uneventfully.

The gross specimen removed at the time of operation (Fig. 2) constituted an interesting picture. The stomach contained two folds of redundant mucosa, the upper of which was 6 cm. long, 3.5 cm. high and, on the average, 6 mm. thick. The lower fold was about 9 cm. long, 4.5 cm. high and, on the average, 6 mm. thick. The folds were involved by chronic gastritis, whereas the rest of the stomach exhibited evidence of atrophic gastritis. Dr. Broders, who examined the operative specimen, thought that the folds represented a developmental anomaly.

### SUMMARY

This case illustrates the difficulty that may be experienced gastroscopically in distinguishing between prolapse of the gastric mucosa (especially when it is involved by gastritis) and gastric carcinoma. It is only by calling attention to cases of this type that we can hope in the future to avoid similar errors.

All too frequently, an attempt is made to establish a definite gastroscopic diagnosis by a single examination. When there is a question of doubt, it is well to employ the Taylor "two-look" technic, and especially to emulate the roentgenologists, who have learned by experience that much may be learned by repeating an examination once, twice or even more times. Whether a second or third gastroscopic examination would have led to a correct diagnosis in this case is open to doubt, since it was the first instance of the condition that we had encountered. In subsequent cases, however, we have experienced no such difficulty.

A technic which we have found of value in cases of this nature is palpation of the abdomen with the hand during the course of gastroscopic observation. This may enable the gastroscopist to obtain some



Fig. 2. Gross specimen, demonstrating character of prolapsed mucosa.

information as to the pliability of the gastric wall, and may assist in bringing portions of the gastric wall into view which otherwise might not be visualized.

### CONCLUSIONS

A case of prolapse of the gastric mucosa of the stomach is presented in which the lesion was misinterpreted gastroscopically as being gastric carcinoma.

Repeated gastroscopic examination undoubtedly will obviate such gastroscopic errors in the future.

Palpation of the abdomen during the process of gastroscopy is undoubtedly of definite value in the gastroscopic study of gastric disease.

### REFERENCES

1. Brunn, Harold and Pearl, Felix: Diffuse Gastric Polyposis—Adenopillomatosis Gastrica. *S. G. O.*, 43:559-598, Nov., 1926.
2. Ellicson, E. L., Pendergrass, E. P. and Wright, V. W. M.: The Roentgen-ray Diagnosis of Pedunculated Growth and Gastric Mucosa Prolapsing Through the Pylorus; Review of the Literature. *Am. J. Roent.*, 15:295-322, 1926.
3. Knott, J. L.: Giant Rugae (Localized Hypertrophic Gastritis) Resembling Carcinoma. *Am. J. Roent.*, 35:204-207, Feb., 1936.
4. Konjetzny, G. E.: Eine besondere Form der chronischen hypertrophischen Gastritis unter dem klinischen und röntgenologischen. *Bilde des Carcinoms. Chirurg.*, 10:260-268, April 15, 1938.
5. Moutier, Francois: Traité de gastroscopie et de pathologie endoscopique de l'estomac. Paris, Masson & Cie, 347 pp., 1935.
6. Pendergrass, E. P.: Prolapse of Pedunculated tumors and Gastric Mucosa Through Pylorus Into Duodenum. *J. A. M. A.*, 94:317-321, Feb. 1, 1930.
7. Schindler, Rudolf: Gastritis Simulating Tumor Formation. *Am. J. Dig. Dis.*, 6:523-529, Oct., 1939.
8. Tynlor, Hermann: Practical Evaluation of Gastroscopy. *Lancet*, 5:131-135, Feb. 1, 1941.

## Benign Submucosal Tumors of the Stomach: A Gastroscopic Study

By

RUDOLF SCHINDLER, M.D.

CHICAGO, ILLINOIS

DAVID J. SANDWEISS, M.D.

DETROIT, MICHIGAN

and

I. LEW MINTZ, M.D.

LOS ANGELES, CALIFORNIA

THE purpose of this paper is to demonstrate that the diagnosis of submucosal benign tumors and their differential diagnosis from benign mucosal tumors (polyps) is possible by gastroscopic observation.

Benign tumors of the stomach have proved to be more frequent and more important than it was believed a few years ago (12, 14, 32, 35.) Benign mucosal tumors originate from the mucosa and protrude into the cavity of the stomach being either broad based or pedunculated. Such protrusions are usually called polyps even if they are not true tumors. These gastric polyps may be inflammatory "pseudo polyps," hyperplastic polyps or true benign adenomas (36.) They are frequently found at gastroscopy but because of their softness the smaller ones are often indiscernible at X-ray relief examination and may be even overlooked at operation. The larger ones can be demonstrated by X-ray examination although their differential diagnosis from malignant tumors may prove to be difficult. Although these mucosal tumors may become important by causing anemia or by obstructing the pylorus or by developing into a carcinoma, the great majority of them are harmless and they may well be watched and treated conservatively.

Benign submucosal tumors may be leiomyomas or fibromyomas, these two types being the most frequent ones; or myxomas, hemangiomas, neurofibromas, lipomas, osteomas, osteochondromas, or lymphomas. A survey on these tumors will be found in the papers of Minnes and Geschickter (23) and of Lahey (18.) Submucosal small fibromyomas are probably frequent. Rieniets (31) was able to find in two hundred consecutive autopsies forty-three leiomyomas in thirty-two stomachs by palpation. These frequent small submucosal tumors, however, are of no practical im-

portance. They make no symptoms and cannot be diagnosed. However, as soon as they protrude the gastric mucosa they become clinically important. All of them have a great tendency to ulcerate and then to bleed profusely. The danger of such hemorrhage is so great that, in our opinion, such a tumor should be extirpated as soon as it is recognized. Therefore, its differential diagnosis is important.

The symptoms are often only syncope, weakness, fatigue, and palpitation with secondary anemia. In some cases the symptoms of a peptic ulcer may be present. Gross hemorrhage, in the form of hematemesis or of tarry stools is the chief symptom, and the recurrence of such hemorrhage is frequent. At least ten cases with fatal hemorrhage have been reported in the literature (3, 13, 14, 20, 25.) Malignant degeneration has been observed, but, in our opinion, it is less frequent and less important than usually assumed. Further clinical detail will be found in the textbook of Eusterman and Balfour (11.) The differential diagnosis between mucosal and submucosal tumors is impossible at X-ray examination, but it can be made at the gastroscopic observation by the symptom of the "bridging folds."

### GASTROSCOPIC OBSERVATIONS

Three cases are presented: only the third case has been proved by surgery and microscopic study.

Case 1. The senior author in 1923 (34) diagnosed a benign submucosal tumor in a patient who had had a severe gross hemorrhage. The cherry sized tumor was seen in the anterior wall immediately beneath the cardia and the colored picture published showed well the reason for diagnosing a submucosal rather than a mucosal tumor, the one sign not compatible with a mucosal tumor and permitting the diagnosis of a submucosal tumor, namely, the stretching of a mucosal fold from the surrounding mucosa up to the surface of the tumor, apparently



Fig. 1. Roentgenogram Case 3. Filling defect of the lesser curvature interpreted as malignancy, but being effected by benign submucosal tumor.

*bridging the space between the top of the tumor and the level of the surrounding mucosa.*

Case 2. A second similar case was observed by us on January 24, 1938. A 63 year-old patient referred by Dr. David Lerner of Chicago, had had four severe gastric hemorrhages in the past two years. X-ray showed a smooth filling defect in the antrum, and because of the clinical picture Dr. Gerhard Danelius, who had made the X-ray picture, suspected this to be a myoma. The gastroscopic protocol read: "The gastroscopic examination was easy; the antrum was seen immediately. Protruding from the anterior wall and greater curvature, a round spherical prominence was seen, the diameter of which was about 3 cm. The mucosa covering the tumor was entirely smooth. Most characteristically, some small folds running from the greater curvature of the antrum to the tumor were stretched by traction . . ." The gastroscopic impression was that of a submucosal benign tumor. The patient refused operation, and hence the diagnosis was not proved.

Case 3. In this third case, operation and subsequent gross and microscopic examination permitted the verifi-

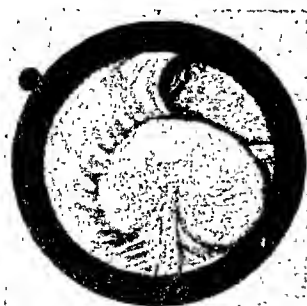


Fig. 2. Gastroscopic picture of a typical submucosal benign tumor. The benignity is apparent from the smooth surface and the entirely sharp limitation. The submucosal location is diagnosed from the presence of many stretched-out folds bridging the recession of the tumor. In the right upper quadrant the antrum and pylorus are seen. The diagnosis was surgically confirmed. (See Figs. 3, 5 and 6.)



Fig. 3. Gross specimen of the tumor demonstrated in Fig. 2. The operation was carried out almost three years after the gastroscopic examination. The ulceration seen on the top of the tumor had probably developed within this period of time. The stretching of the folds does not come out very well in this gross specimen.

cation of the previously made gastroscopic diagnosis of a benign submucosal tumor. A 53 year-old male patient was first seen by one of us (D. J. S.) on March 30, 1936, with complaints of intermittent attacks of heartburn coming on one hour after meals, and nausea, and heavy feeling in the epigastrium after meals. The physical examination was essentially negative. There was free hydrochloric acid in the gastric contents. The pain disappeared when the patient was put on a bland diet. On 12/20/36 the patient returned because he suddenly experienced acute distress followed by weakness and dizziness. The stools were tarry, containing blood. He was hospitalized and put on a standard Sippy regimen. Epigastric distress did not disappear entirely. One month later an X-ray examination was carried out. A constant defect was noted in the lesser curvature of the pars media, suspicious of malignancy (Fig. 1.) Gastroscopy was then advised and undertaken on February 20, 1937 (R. S.) Fig. 2.) The protocol read as follows: ". . . Above the angulus a tumor was seen. Its long diameter extended in the direction from the lesser to the greater curvature. It was covered with smooth mucous membrane. All around there was a recess between



Fig. 4. Gross specimen of another benign submucosal tumor (leiomyoma), due to the courtesy of Dr. Moses Steinberg of Portland, Oregon, which shows the bridging mucosal folds (arrow.) This tumor was ulcerated, also, and gross hemorrhage led to surgery.





Fig. 5. Gross specimen of the submucosal benign tumor demonstrated in Figs. 2 and 3. Perpendicular section demonstrating the submucosal location, the superficial ulceration and the extensive necrosis.

the surface of the tumor and the surrounding mucosa, but some folds running along the anterior wall were seen to bridge this recession and to spread onto the surface of the tumor. The diameter of the tumor was estimated to be 4 cm."

The gastroscopic impression was "Benign submucosal tumor of the anterior wall."

Surgery was advised but the patient refused. In December, 1939, the patient developed a hemorrhage similar to the first one. The bleeding this time did not stop, in spite of therapy, and therefore, the patient finally consented to operation.

In January, 1940, a subtotal resection of the stomach was carried out by Dr. C. Fremont Vale of Detroit, Michigan. A benign submucosal tumor was found, measuring 3.5 cm. in diameter (Fig. 3.) It was covered by smooth mucosa, but at the summit of the protuberance there was a deep ulceration. Although the gross specimen as pictured in Fig. 3 shows some folds running toward the tumor, their specific character bridging the recession of the tumor cannot be recognized very well, probably because the tissue has lost its elasticity. However, Fig. 4 shows a similar tumor sent us by Dr. Moses Steinberg of Portland, Oregon, in which the characteristic bridging or stretching of the folds can be recognized. This phenomenon can be seen still better in a picture published by Eusterman and Balfour (11—page 555, Fig. 285),

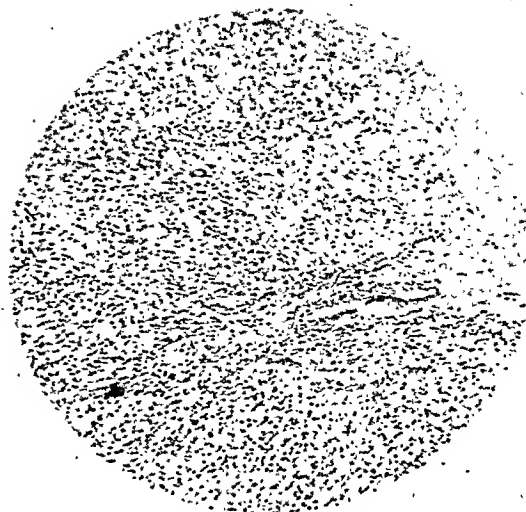


Fig. 6. Photomicrograph of a microscopic section through the benign submucosal tumor demonstrated on Figs. 1, 3 and 5, revealing a myxofibroma.

and in the picture of a submucosal gastric lipoma, published by M. J. Rumold (33.)

Fig. 5 is a perpendicular section through our own tumor showing well the submucosal character, the superficial ulceration, and the extensive area of necrosis which obviously had led to the repeated hemorrhages. Microscopically (Fig. 6) this tumor was a myxofibroma, a rather rare form of submucosal gastric tumor, reported, however, by Moore (27) and Judd and Hoerner (15).\*

### SUMMARY

(1) The diagnosis of submucosal benign gastric tumors is possible at gastroscopy by a characteristic sign described in this paper.

(2) The importance of this diagnosis is emphasized. Submucosal benign tumors have a great tendency to bleed profusely and even fatally and should be removed as soon as the correct diagnosis has been made.

\*The patient has had no gastro-intestinal symptoms since gastric resection was performed. Last contact was December 23, 1941, two years after gastric resection.

### REFERENCES

1. Allen, L. G. and Hiebert, M. D.: Myosarcoma of the Stomach. *Radiology*, 32:567-572, May, 1939.
2. Ball, G.: Leiomyoma of the Stomach. *Brit. J. of Surgery*, 25:942-944, April, 1932.
3. Bland-Sutton, Sir John: Fibroids, Lipomas, Dermoids and Polypi of the Stomach and Intestine. *Lancet*, 2:7, 1920.
4. Brayne, F. F. and Simon, A. L.: Pedunculated Submucous Fibromyoma of the Stomach. *Brit. Med. J.*, 1:920, 1927.
5. Buckstein, Jacob: Clinical Roentgenology of the Alimentary Tract. W. B. Saunders Co., Phila., Pa., 1940.
6. Cabot, R. C.: Leiomyosarcoma of the Stomach. *New Eng. J. Med.*, 220:351-353, Feb. 23, 1939.
7. Collins, F. K. and Collins, D. C.: The Surgical Significance of Gastric Leiomyomas. *Western J. of S. G. O.*, 46:185, 1938.
8. Conway, J. H.: Leiomyoma of the Stomach. *Arch. Surg.*, 33: 792-807, Nov., 1936.
9. Down, H. I.: Leiomyoma of the Stomach Associated with Gastric Hemorrhage. *Proc. of Staff Meet., Mayo Clinic*, 5:353, Dec. 17, 1936.
10. Eliason, E. L. and Wright, V. W. M.: Benign Tumors of the Stomach. *S. G. O.*, 41:461-472, 1925.
11. Eusterman, G. B. and Balfour, D. C.: The Stomach and Duodenum. W. B. Saunders Co., Phila., Pa., 1935.
12. Eusterman, G. B. and Senty, E. G.: Benign Tumors of the Stomach. *S. G. O.*, 34:5-15, 1922.
13. Ewing, J.: Neoplastic Diseases. Fourth Ed., W. B. Saunders Co., Phila., Pa., 1940.
14. Hunt, V. C.: Benign Tumors of the Stomach. *Surgery*, 1:711, 1937.
15. Judd, E. S. and Hoerner, M. T.: Benign Tumors of the Stomach. *Am. J. Surg.*, 31:427-430, 1936.
16. Kahn, M.: Endogastric Myoma. *Surgical Clinics North America*, 10:1073, 1930.
17. Kirklin, B. R. and Weber, H. M.: Roentgenologic Diagnosis of Neoplastic Diseases of the Stomach. *Am. J. Cancer*, 16:1134, 1932.
18. Lahey, O. H. and Colecock, B. P.: Diagnosis and Surgical Management of Leiomyomata and Leiomyosarcomata of the Stomach. *Ann. Surg.*, 112:671-685, Oct., 1940.
19. Lockwood, B. C.: Benign Tumors of the Stomach with Report of Cases. *J. A. M. A.*, 98:969-973, March 19, 1932.
20. Melnick, P. J.: Metastasizing Leiomyoma of the Stomach. *Am. J. of Cancer*, 16:890-902, 1932.
21. Meyer, K. A. and Singer, H. A.: Intermittent Gastric Ileus Due to Mechanical Causes. *S. G. O.*, 53:742-749, 1931.
22. Meyer, K. A. and Rosi, P. A.: Leiomyoma of the Stomach. *Surg. Clin. North America*, 13:1245-1249, 1933.
23. Minnes, J. F. and Geschickter, C. F.: Benign Tumors of the Stomach. *Am. J. of Cancer*, 25:136-149, 1936.
24. Mock, H. E. and Lindquist, J. L.: Gastric Leiomyoma. *North-west Med.*, 36:42-44, 1937.
25. Morgan, D. G.: Hemorrhage and Death from a Gastric Myoma. *Brit. Med. J.*, 2:15, 1931.
26. Mott, V. W.: Benign Tumors of the Stomach. *Rev. of Gastro-Enterol.*, 4:297, 1937.
27. Moore, A. B.: Benign Tumors of the Stomach from the Roentgenologic Point of View. *J. A. M. A.*, 89:368-370, 1927.
28. Moutier, F.: *Traité de Gastroscopie*. Masson-Paris, 1935.
29. Nelson, H. G. G.: A Partially Ossified Fibroma of the Stomach Wall. *Brit. J. Surg.*, 18:660, 1931.
30. Redell, G.: On Benign Submucous Tumors of the Stomach. Particularly Lipoma. *Acta Chir. Scandinav.*, 51:323-342, 1935.



31. Rieniets, J. H.: The Frequency and Pathologic Aspects of Gastric Leiomyoma. *Proc. Staff Meet., Mayo Clinic*, 5:50-56, Dec. 17, 1930.
32. Rigler, L. R. and Eriksen, L. G.: Benign Tumors of the Stomach. *Radiology*, 25:6-15, 1936.
33. Rumold, M. J.: Submucous Lipoma of the Stomach. *Surgery*, 10:242, 1941.
34. Schindler, Rudolf: *Lehrbuch und Atlas der Gastroskopie*. Munich, I. F. Lehmann, 1923.
35. Schindler, Rudolf: *Gastroscoy: The Endoscopic Study of Gastric Pathology*. Chicago, University of Chicago Press, 1937.
36. Schindler, Rudolf and McGlone, F.: Familial Occurrence of Hyperplastic Gastric Polyps: A Report of Two Cases, Classification of Benign Mucosal Tumors of the Stomach. *Arch. Surg.*, 41:1483, 1940.
37. Stewart, M. J.: The Relation of Malignant Disease to Benign Tumors of the Intestinal Tract. *Brit. Med. J.*, 2:567-569, 1929.
38. Tayama, M.: Myoma Case. *Zentralblatt f. Chir.*, 65:2560, Nov. 12, 1938.

## The Mode of the Laxative Action of Phenolphthalein

By

PHILIP BLICK, Ph.D., J. B. BERARDI, M.D.

and

OSKAR WOZASEK, M.D.

CHICAGO, ILLINOIS

**P**HENOLPHTHALEIN is generally classified as an "irritant" cathartic along with such substances as Cascara sagrada, Castor oil, and Mercurous chloride. These are said to produce catharsis by "irritation" of the intestinal mucosa or by increasing the motor activity of the intestine. The increase in motor activity may involve either the nervous mechanism or musculature, or both.

"Irritation" is a loosely used and rather indefinite term. We have no accurate measure for it. When applied to the intestine, Fantus et al (1) took as a measure of irritation, the appearance of mucous strings and protein in the stool. The normal stool, they found, contains less than 0.1 cc. mucus per gram, no mucous strings and no protein. If the mucus content exceeds this amount, it is an indication of hypersecretion; if strings and protein appear, it is a sign of irritation. Even though this may appear to be a rather arbitrary standard and perhaps too delicate a test, their following conclusions are pertinent:

"The appearance of mucus in strings or membranes in stool smears is abnormal. This may be a sign of an irritable colon when found intermittently. It indicates a definite lesion of the colon when present constantly.

Marked presence of unchanged leukocytes in stool smears indicates inflammatory or ulcerative colitis.

Protein in feces is an abnormal finding. It is found in cases of severe colitis and intestinal bleeding."

The boundary between stimulation and irritation is quite debatable ground. An irritant suggests something that elicits some signs of inflammation and suggests danger. If an irritant is sufficiently weakened, however, it may become a stimulant.

After the use of phenolphthalein in varying doses and in a large number of normal and constipated cases, Fantus and co-workers found no signs of irritation in the proper use of the term by their and other rigid standards\*; therefore, it may be that phenol-

phthalein is not an irritant, but that it is more correctly an intestinal stimulant.

### *Local Action in the Intestines*

Daguin (2) studied the mechanism of phenolphthalein by placing it in loops of rabbit's intestine. He found that phenolphthalein caused increased peristaltic intestinal movement.

By injection of phenolphthalein into the ear vein, he obtained negative results. There was no effect on the circulation, respiration, renal secretion, or the neuromuscular system. He concluded that phenolphthalein acts directly on the intestine to increase contractility.

Abel and Rowntree (3) found that very large doses injected intravenously had scarcely any effect on the blood pressure. We have confirmed these findings. This indicates that there can be but very slight "irritative effect," and practically no action on the nerves.

Larson and Barger (4), from a study of the action of cathartics (including phenolphthalein) on isolated colon of the dog, concluded that increased mucus is due to increased movements of the wall concomitant with the process of defecation and that increased mucus is evidence of "irritative" action of the drug. They further state that there is no evidence that a separate nervous reflex is involved in this secretion. This would agree with our conclusion that phenolphthalein acts directly on the muscle.

A recent Russian publication (5) indicates that irritation may occur in some special tissues but only after extremely large amounts. They found that huge doses of phenolphthalein, equivalent to 200 Gm. for a man, injected *subcutaneously* into mice, white rats, rabbits and frogs, caused no laxative effect in any of the animals, but "irritated" the urinary bladder and alimentary canal in frogs. From such experiments no conclusion of value may be drawn regarding the mode of action of phenolphthalein.

### *Site of Action*

From X-ray studies Caldwell and Crane (6) offer the following conclusions regarding phenolphthalein. In ordinary dosage the drug has no appreciable effect on the movements of the stomach or the small intestines. Phenolphthalein does not directly affect the rate of movement of the food material in any part of the digestive tract taken simultaneously with it. The proximal half of the colon shows very little, if any,

\*To be published.

From the Department of Pharmacology and Therapeutics, H. A. McGuigan, Ph.D., M.D., Head of the Department, University of Illinois College of Medicine.  
Aided by a grant from the Phenolphthalein Research, Inc.  
Submitted February 5, 1942.

increase in its motor activity during the period in which phenolphthalein is most active—about 8 to 12 hours after it is taken. The movements of the distal half of the large intestine are strongly stimulated by phenolphthalein during its active period. It has no local effects in any portion of the alimentary canal due to chemical or mechanical action on the bowel wall. The drug is in part absorbed during its passage through the small intestine and re-excreted into the colon or large bowel. The laxative properties of phenolphthalein are due chiefly, if not entirely, to the stimulation of the large bowel by that portion of the drug which is absorbed and carried by the blood to this portion of the tract. Only that portion of the intestinal contents which has reached the distal colon by the time the phenolphthalein becomes active, viz., about 8 to 12 hours after its ingestion, is directly influenced by it. Other apparent effects are secondary and indirect according to the authors.

Ott and others (7) studied the action of phenolphthalein on pieces of intestine of cats and rabbits. (1) the Cambridge intestinal plethysmograph and Dr. Schlayer's recording apparatus by which the blood pressure is also being recorded and (2) the Magnus method. His studies show that phenolphthalein causes an increase in intestinal motility resembling mild stimulation. Unfortunately, no conclusion can be drawn from his results whether this stimulation is due to action on the muscles or on the nerves.

Kegerreis (8) in this laboratory has shown by X-ray studies in human being that a dose of 0.30 Gm. (5 gr.) phenolphthalein speeds up intestinal movement about 10%. A dose twice this size hastens the action still more. This, we think, in conjunction with the work of Ott and Scott, shows that phenolphthalein may act on the musculature of the gut in all locations. That phenolphthalein mildly stimulates intestinal movements is beyond dispute. Our present work is

concerned with the "irritant action" and with the site of action.

## METHODS

### I. Local Action when Introduced Into Moreau Loops in Dogs

When large doses (0.5-1 Gm.) are introduced into Moreau loops in dogs, some is absorbed as shown by tests of the blood. All of the fluid introduced with the drug may be absorbed. The loop may be contracted quite strongly, but there were no visible signs of irritation such as redness or congestion. The gross appearance therefore, indicates contraction only. Whether this contraction is purely due to muscular action, or whether the nerves are also involved, this experiment cannot show.

The results of the examination of the contents of Moreau loops, in which phenolphthalein or other cathartics had been introduced, are shown in Table I, II and III. They show by our standard that even in large doses, phenolphthalein is not irritant in the proper use of that term.

### II. Phenolphthalein Action or Nonaction on the Nerves

Evidence of action or nonaction on the nerves may be obtained by use and comparison of the effects of phenolphthalein alone and combined:

1. with atropine and
2. with pilocarpine or eserine which act on the nerves, and
3. by comparison with Ba Cl<sub>2</sub> and pituitrin preparations that act only on the muscle.

### Effect of Atropine on Phenolphthalein Action

Fantus and Dyniewicz in this laboratory (unpublished work) studied 150 human cases. About 6 per cent of these, after taking 0.060 Gm. phenolphthalein, had cramps of varying degrees. With larger doses the incidence of cramps increased. Atropine in one milligram doses, which had a definite effect pro-

TABLE I  
Findings in intestinal loops 2 hours after local application of phenolphthalein and other drugs

| Type of Drug Used<br>in 5 cc. Amounts       | Loop Contents<br>in Grams | Chemical                  |                             | MICROSCOPIC  |         |                        |     |     |
|---|---------------------------|---------------------------|-----------------------------|--------------|---------|------------------------|-----|-----|
|   |                           | Mucus<br>cc. Per<br>1 Gm. | Protein<br>cc. Per<br>1 Gm. | Carmin Stain |         | Giemsa Stain for Cells |     |     |
|   |                           |                           |                             | Mucus        | Strings | Epithelial             | WBC | RBC |
| 5% Phenolphthalein                          | 0                         | —                         | —                           | +            | +       | ++                     | 0   | 0   |
| 5% Phenolphthalein                          | 0                         | —                         | —                           | +            | +       | ++                     | 0   | 0   |
| 5% Phenolphthalein                          | 0                         | —                         | —                           | +            | 0       | +                      | 0   | 0   |
| 5% Phenolphthalein                          | 0                         | —                         | —                           | +            | 0       | +                      | 0   | 0   |
| 5% Phenolphthalein                          | 0                         | —                         | —                           | +            | 0       | +                      | 0   | 0   |
| 20% Magnesium<br>Sulfate Cascara<br>Sagrada | 13.12<br>+ (cascara)      | 0                         | 0                           | +            | +       | +++<br>+               | +   | 0   |
| 5% Barium Sulfate                           | 0                         | —                         | —                           | +            | 0       | +++                    | 0   | 0   |
| 15% Sodium Chloride                         | 20.16                     | +++                       | .20                         | +            | +       | +++                    | +   | +   |
| 1% Calomel                                  | 0.91                      | .08                       | .70                         | +            | +       | +++                    | 0   | 0   |
| 5% Glycerin                                 | 15.67                     | .08                       | 0                           | +            | ++      | +++*                   | 0   | 0   |
| 5% Bismuth<br>Subgallate                    | 0                         | —                         | —                           | +            | 0       | +                      | 0   | 0   |
| 5% Tannic Acid                              | 7.54                      | +++                       | +                           | +            | 0       | +++**                  | +   | 0   |

\*Cells in connection and tissue particles.

\*\*Cells changed.

\*\*\*Incomplete precipitation.

ducing dry mouth and throat, coughing, etc., had no definite action in relieving the cramps or in delaying significantly the action of phenolphthalein. These results support the opinion that phenolphthalein acts directly on the muscular tissue.

#### *Effect of Phenolphthalein on the Vagus Mechanism in Dogs*

Dogs were anesthetized with sodium pentobarbital (35 mgm./Kg. body weight) given intraperitoneally and prepared in the usual manner for blood pressure, respiration, electrocardiogram and bowel tracing. With this anesthetic, the blood pressure remains practically normal indicating little if any action on motor nerves. Both vagi nerves were exposed for electrical stimulation. A balloon was placed in the distal part of the ileum for bowel peristaltic study. Phenolphthalein solution, 4.2% in 70% Ethyl alcohol was then injected into the femoral vein continuously by means of a burette at the rate of 1 cc. per minute until the total lethal dose had been given.

Control electrocardiograms were taken before the injection of phenolphthalein, also during the stimulation of the right and left vagus nerves. After the injection of phenolphthalein, electrocardiograms were taken every 10 minutes before, during, and after the stimulation of both vagi nerves.

#### *Results:*

There was no increase in the activity of the gut noticed as registered by the tambour connected to the balloon in the small gut after a period of 2 hours. There was noted, however, increased peristalsis in the large bowel. There was no change in the strength of current, necessary to arrest the heart.

Eserine was then injected, 1 mgm. intravenously. There was marked activity of peristalsis of the small bowel which was increased by electrical stimulation of both vagi nerves, and a weaker current produced more effect after eserine. Further injection of phenolphthalein did not alter the activity of the small bowel.

The eserine produced marked slowing of the heart with an initial rise in blood pressure followed by a progressive but gradual drop. There was marked slowing in the respiratory rate following the eserine injection.

Suspensions of phenolphthalein in water and injected in doses of 1 Gm. directly into the first portion of the jejunum in animals prepared as above, during and for a period of 3 hours did not affect the bowel locally, but did increase the action of the large bowel after several hours. The findings hence were essentially the same as when the drug was given intravenously.

Phenolphthalein produced no changes on the vagus mechanism of the heart. Electrical stimulation of the vagus nerve with the same strength of current, produced cardiac standstill before and after phenolphthalein. Phenolphthalein produces a slight drop in blood pressure, but very little change in pulse pressure. Respiration becomes slower and irregular. Respiration stops before the heart; changes in the electrocardiogram are slight and only in large doses does it produce slight auricular irregularities and increase in amplitude of the P-waves. Phenolphthalein in alcohol given until the death of the animal kills by the effect of the alcohol on the respiratory center.

#### *Comment:*

The intravenous injection of phenolphthalein does not increase the peristaltic activity of the small intestine in dogs. It does increase the activity of the large bowel as could be seen. It has no action on the parasympathetic nerves of the heart. It does not produce any changes in the vagus mechanism as noted on the electrocardiogram which would support the view that it does not act on the nerve.

#### EFFECT OF BARIUM CHLORIDE ON THE ELECTROCARDIOGRAM

Barium chloride injected intravenously in 10 mgm. doses in dogs, produced marked changes in the electro-

TABLE II  
*Findings in intestinal loops 2 hours after parasympathetic acting (muscular acting Ba Cl<sub>2</sub>) drugs given intravenously*

| Drug                                  | Loops              | Loop Contents in Grams | Chemical            |                       | MICROSCOPIC  |         |                        |     |     |
|---------------------------------------|--------------------|------------------------|---------------------|-----------------------|--------------|---------|------------------------|-----|-----|
|                                       |                    |                        | Mucus cc. Per 1 Gm. | Protein cc. Per 1 Gm. | Carmin Stain |         | Giemsa Stain for Cells |     |     |
|                                       |                    |                        |                     |                       | Mucus        | Strings | Epithelial             | WBC | RBC |
| 3 mg. Atropin i.v.                    | 5 cc. Saline       | 0                      | —                   | —                     | +            | 0       | +++                    | +   | ++  |
|                                       | 5 cc. Phenolph. 5% | 0                      | —                   | —                     | +            | 0       | +++                    | +   | ++  |
|                                       | Empty              | 0                      | —                   | —                     | 0            | 0       | +++                    | +   | +   |
| 0.75 mg. Physostigmin i.v.            | 5 cc. Saline       | 1.94                   | .02                 | 0                     | +            | +       | +                      | +   | 0   |
|                                       | 5 cc. Phenolph. 5% | 4.26                   | .04*                | 0                     | +            | 0       | +                      | +   | 0   |
|                                       | Empty              | 1.33                   | .04                 | 0                     | +            | 0       | ++                     | 0   | 0   |
| 1.2 mg. Physostigmin (subcutaneously) | 5 cc. Saline       | 0.90                   | .03                 | 0                     | +            | 0       | +                      | 0   | 0   |
|                                       | 5 cc. Phenolph. 5% | 0.94                   | .06                 | 0                     | +            | 0       | +                      | 0   | +   |
|                                       | Empty              | 1.2                    | .04                 | 0                     | +            | 0       | +                      | 0   | 0   |
| 1 mg. Pilocarpin i.v.                 | 5 cc. Saline       | 4.94                   | .05                 | .08                   | +            | +       | ++                     | 0   | 0   |
|                                       | 5 cc. Phenolph. 5% | 4.86                   | .05*                | .08                   | +            | 0       | ++                     | 0   | 0   |
|                                       | Empty              | 5.61                   | .04                 | 0                     | +            | 0       | +                      | 0   | 0   |
| 1% Barium Chloride 5x1 cc. i.v.       | 5 cc. Saline       | 6.61                   | .03                 | .08                   | +            | 0       | ++                     | 0   | 0   |
|                                       | 5 cc. Phenolph. 5% | 7.35                   | .05                 | .05                   | +            | 0       | +++                    | 0   | 0   |
|                                       | Empty              | 5.34                   | .06                 | .20                   | ++           | 0       | ++++                   | 0   | 0   |

\*Incomplete precipitation.

cardiogram—pulsus bigeminus—and a characteristic rise in blood pressure. These changes are presumably due to an action on the muscle, since barium acts on all types of muscle irrespective of the innervation. After 5 cc. 1% barium chloride was injected into a Moreau loop, the intestines contracted into circular folds without shortening. The mucosa was wet and glistening.

From the above we can draw the conclusion that phenolphthalein simulates the barium action on the gut. Barium, however, is much stronger in action on the muscle than is phenolphthalein, and affects the heart muscle, while phenolphthalein has no demonstrable action on the heart.

#### EFFECT OF PITUITARY PREPARATIONS, PITRESSIN, PITOCIN AND PITUITRIN ON THE BOWEL, BLOOD PRESSURE, AND THE ELECTROCARDIOGRAM

To compare the effects of pituitary preparations on the bowel, the blood pressure, and the electrocardiogram, dogs were anesthetized as described and prepared for blood pressure, respiration, electrocardiographic tracings, (using Lead II only) and for intestinal peristalsis recordings. The intestinal activity was recorded by means of a balloon inserted into the distal ileum about six inches above the cecal junction.

Electrocardiograms were taken before, during and

after injecting 1 cc. of the respective preparation intravenously.

**Pitressin:** The effects of pitressin on the blood pressure depend on the rapidity of the injection. Injections of 1 cc. over a period of ten minutes produced a slight rise in blood pressure followed by a return to normal. Injections of 1 cc. over a period of five minutes produced a slight rise in blood pressure followed by a marked drop, a subsequent rise and a return to normal. Injections of 1 cc. given rapidly produced a slight initial rise in blood pressure followed by a marked drop, rapid respiration and death if adrenalin was not immediately given intravenously. Pitressin caused a slowing in heart rate and characteristic changes in the T-wave of the electrocardiogram. The changes in the T-wave consisted of increased voltage with high take-off and increased ST interval. Intestinal activity was markedly increased when injection was given rapidly, and less so when given slowly. When adrenalin 1 cc., 1:1000 solution was injected intravenously, at the height of peristaltic activity of the bowel, there occurred an immediate slowing of peristalsis and finally a complete arrest of all bowel activity.

**Pitocin:** There was no change noted in the systolic blood pressure; there was a slight decrease in the diastolic pressure, thus producing an increase in pulse pressure. No change noted in respiration. The electrocardiogram revealed a slowing of the heart rate with a slight increase in the amplitude of the T-waves.

TABLE III

Findings in intestinal loops 2 hours after parasympathetic acting (muscular acting  $Ba Cl_2$ ) drugs applied locally

| Loops  | Loop Contents in Grams | Chemical            |                       | MICROSCOPIC  |         |                        |     |     |
|--|------------------------|---------------------|-----------------------|--------------|---------|------------------------|-----|-----|
|  |                        | Mucus cc. Per 1 Gm. | Protein cc. Per 1 Gm. | Carmin Stain |         | Giemsa Stain for Cells |     |     |
|  |                        |                     |                       | Mucus        | Strings | Epithelial             | WBC | RBC |
| 3 mg. Atropin in 5 cc. Saline                        | 0                      | —                   | —                     | +            | 0       | +                      | 0   | 0   |
| 3 mg. Atropin in 5 cc. Phenolphthalein Emulsion      | 0                      | —                   | —                     | +            | 0       | +                      | 0   | 0   |
| (5 cc. Saline)                                       | 0                      | —                   | —                     | +            | 0       | ++                     | ±   | 0   |
| Control (Empty)                                      | 0                      | —                   | —                     | +            | 0       | ++                     | 0   | 0   |
| 2 mg. Physostigmin in Saline                         | 3.05                   | .05                 | .15                   | +            | +       | +                      | +   | +   |
| 2 mg. Physostigmin in 5 cc. Phenolphthalein Emulsion | 4.59                   | .02                 | .22                   | +            | +       | ++                     | 0   | 0   |
| (5 cc. Saline)                                       | 0                      | —                   | —                     | +            | +       | ++                     | 0   | 0   |
| Control (Empty)                                      | 0                      | —                   | —                     | +            | +       | ++                     | 0   | 0   |
| 2 mg. Pilocarpin in 5 cc. Saline                     | 2.08                   | .01                 | .02                   | +            | +       | +                      | 0   | 0   |
| 2 mg. Pilocarpin in 5 cc. Phenolphthalein Emulsion   | 5.39                   | .10                 | .15                   | +            | 0       | ++                     | 0   | 0   |
| (5 cc. Saline)                                       | 0                      | —                   | —                     | +            | 0       | ++                     | ±   | 0   |
| Control (Empty)                                      | 0                      | —                   | —                     | +            | 0       | ++                     | 0   | 0   |
| 5 cc. 1% Barium Chloride                             | 5.99                   | .05                 | .01                   | +            | 0       | +                      | ±   | ±   |
| 5 cc. 5% Phenolphthalein Emulsion                    | 0.77                   | .10                 | .10                   | +            | +       | +                      | +   | +   |
| 5 cc. Saline   | 1.07                   | .04                 | .01                   | +            | 0       | ++                     | 0   | 0   |

\*Cells in connection.

There was a complete inhibition of intestinal activity. After complete inhibition of intestinal activity 2 mgm. of eserine was injected intravenously. There was marked increase in blood pressure, marked slowing of the heart rate, increase in voltage of the T-waves, and the QRS-complex became diphasic. The intestinal activity became increased.

*Pituitrin:* This drug produced an increase in blood pressure and a slowing of respiration. The electrocardiogram revealed a slowing in heart rate and a very slight increase in amplitude of the T-wave. There was no appreciable change in bowel activity noted.

#### *Effect of Pituitrin on the Contents in Moreau Loops*

(a) Intravenous Injection of Pituitrin: Three loops of 5 inch length were prepared in the lower ileum of a dog under sodium pentobarbital anesthesia. The proximal loop was left empty; in the middle loop 5 cc. 5% phenolphthalein emulsion was filled and in the distal 5 cc. physiologic saline solution; 1 cc. pituitrin was injected intravenously. The intestines were inspected from 10 to 15 minutes during the experiment through the laparotomy wound. No marked increased peristaltic movements could be observed. Two hours after the injection the loops were taken out. All of the 3 loops contained some muco-feculent material. Protein was negative in all of them. Microscopic smears showed a considerable amount of epithelial cells and with Carmin stain secretion but no strings in any smear of one of the 3 loops. There were no marked differences between the findings in the phenolphthalein and the control loops. Two hours after intravenous injection no marked contraction or changes in size of the isolated loops could be observed.

(b) Local Application: Four Moreau loops were prepared. (1) One loop was injected with 1 cc. pituitrin and 4 cc. 5% phenolphthalein emulsion, (2) a control loop containing 5 cc. saline solution (control 1.) Loop No. 3 contained 1 cc. pituitrin and 4 cc. saline, and loop No. 4 was left empty (control 2.) After two hours the loops were examined; with the exception of the phenolphthalein loop, which contained some emulsion of phenolphthalein, the loops were empty. Microscopic smears from mucosa of all the loops showed numerous epithelial cells and stringy mucus. The pituitrin and pituitrin-phenolphthalein loops were markedly shortened and their mucosa was in circular folds. The control loops were unchanged.

### DISCUSSION

The mode and site of action of phenolphthalein in producing a laxative effect has not been definitely settled. Text books of pharmacology usually dismiss the subject briefly by stating that phenolphthalein has a mild irritant action and that it acts mainly on the large bowel. The objective findings of bowel irritation, as laid down by Fantus et al, from a study of hundreds of patients, are not produced by phenolphthalein. These clinical results are confirmed experimentally by the local application of phenolphthalein into Moreau loops, when it was found that the contents of the phenolphthalein loops showed no more signs of irritation than the control loops and definitely less than loops containing other cathartics (Table I, II, III.)

The statement of previous workers that phenolphthalein acts locally on the intestine is confirmed by our experiments. In addition, we present evidence

that the phenolphthalein effect is obtained by its stimulating action primarily on the intestinal musculature rather than by its action on the nervous mechanism with secondary effect on the musculature. We base our statements on such facts as: the administration of atropine, which paralyzes the motor nerves of the intestine, does not stop the phenolphthalein effect. Secondly, phenolphthalein did not seem to effect the parasympathetic nerves as judged by its negative effects (in the dog) on the blood pressure and electrocardiogram. Thirdly, that phenolphthalein has a similar effect on the intestinal musculature, even though to a much lesser extent, as does barium chloride and the pituitary preparations (pitressin, pitocin, pituitrin) all of which act on the musculature. Fourthly, phenolphthalein does not apparently modify the effects of eserine—a drug which stimulates the intestine through the nerves.

We used pituitary preparations because so far as we know they act directly on the musculature and their action is not related to innervation. Unfortunately, their action on the intestinal tract is not definitely known; neither is it constant or reliable. Melville and Stehle (9) think the effects obtained depend on the technique of study. In the normal dog without anesthesia by X-ray study they noted increase in bowel activity with the pressor substance, and complete relaxation of the small intestine with the oxytocic substance. They, therefore, concluded that while defecation may be produced by both substances their mode of action is different, but the difference they could not explain.

The mode of action of posterior pituitary extract on the cardiovascular system also has not been definitely determined, and we are unable to correlate its action on the heart, and intestine, in a manner to be valuable in analyzing the action of phenolphthalein on the intestine. There has been a definite consensus of opinion that certain changes in the T-wave of the electrocardiogram occur. How these changes occur is a controversial matter. There have been various reasons proposed such as vagus action, vagal reflex, direct myocardial action, coronary constriction and direct action on the myocardium.

We found that pitressin stimulates the intestinal muscles and increases peristalsis. This stimulation is abolished by adrenalin administration which we would explain by a lessening of the tone of the muscle, through nervous influence. Strong, direct muscular stimulant such as barium chloride would still be effective. Weak muscular stimulant such as phenolphthalein may not be strong enough to remove such inhibition.

Pitocin inhibits muscle activity of the intestine. This inhibition may be prevented by the injection of eserine similarly as after phenolphthalein injection. Pituitrin when given intravenously produces no appreciable stimulation or inhibition of activity of the intestinal musculature. This may be due to the antagonistic action of the pressor and oxytocic substances which it contains.

Pitressin produces a drop in blood pressure and changes in T-wave of the electrocardiogram by decreasing the efficiency of the myocardium resulting from anoxemia secondary to coronary constriction.

That there is a general anoxemia is demonstrated by the marked increase in the respiratory rate. Adrenalin prevents or reverses these reactions.

Pitocin produces no appreciable change in blood pressure and a very slight increase in voltage of the T-wave.

Pituitrin produces a slight rise in blood pressure probably due to a general vasoconstriction, produces a slowing of the heart rate and respiration. The effects on the T-wave of the electrocardiogram are very slight, less than that produced either by pitocin or pitressin. While pituitrin may act on musculature only, the complexity of the effects obtained though similar in many respects to those of phenolphthalein, do not permit us to draw any definite conclusion regarding the site of action of phenolphthalein.

### CONCLUSIONS

1. Phenolphthalein is not an intestinal irritant as judged by the standards we have given.

2. That phenolphthalein acts directly on the muscle is supported by the following facts:

(a) Atropine which paralyzes the motor nerves of the intestine does not stop the cathartic action of phenolphthalein.

(b) Phenolphthalein does not affect parasympa-

thetic nerves as judged by its effect of these nerves on the heart.

(c) Drugs like eserine which stimulate the intestine through the nerves, also effect the vagus to the heart in a similar manner.

3. Barium or pituitrin, which act on musculature applied locally, effect the intestine in a manner similar to, but more markedly than phenolphthalein.

### REFERENCES

1. Fantus, B., Wozasek, O. and Steigmann, F.: Studies on Colon Irritation—Examination of Feces. *Am. J. Dig. Dis.*, Vol. 8, 8:296-298, Aug., 1941.
2. Daguin, A.: Action de la Phenolphthalein sur la Contractilite et la Secretion Intestinales. *Compt. rend. Soc. de Biol.*, 64:153-155, 1908.
3. Abel, J. J. and Rowntree, L. G.: On the Pharmacological Action of Some Phthaleins and Their Derivatives, with Especial Reference to Their Behavior as Purgatives. *J. Pharm. and Exp. Therap.*, 1:231-264, 1909.
4. Larson, L. M. and Bergen, J. A.: Action of Cathartics on Isolated Dog's Colon. *Arch. Surg.*, 27:6, 1120-1145, Dec., 1933.
5. Voronstov, V. N.: Duration of Phenolphthalein Excretion Through Animal Intestines. *Farmakol. i Toksikol.*, 3, No. 5, 3:7, 1940. From Chemical Abstracts, No. 20, 35:7033, Oct., 1941.
6. Caldwell, G. H. and Crane, A. W.: The Influence of Phenolphthalein on Intestinal Movements. *Radiology*, 13:403-412, Nov., 1929.
7. Ott, I. and Scott, J. C.: The Action of Phenolphthalein, Cascara Sagrada and Ergot Upon the Intestinal Movements. *Med. Bul. Med. and Surg.*, No. 1, XXX:90-92, March, 1908.
8. Kegerreis, R.: A Method of Determining and Recording Human Intestinal Motility. *Am. J. Dig. Dis. and Nutrit.*, No. 7, 4:432-438, Sept., 1937.
9. Melville, K. J. and Stehle, R. L.: Actions of Pituitary Preparations (Posterior Lobe) Upon Intestines of Dogs. *J. Pharmacol. and Exper. Therap.*, 50:165-173, Feb., 1934.

## The Effect of Gastric Hypersecretion on the Reaction and Neutralizing Ability of the Contents of the First Part of the Duodenum in Normal Dogs\*†

By

J. EDWARD BERK, M.D., M.Sc. (Med.)‡ J. EARL THOMAS, M.D.

and

M. E. REHFUSS, M.D.

PHILADELPHIA, PENNSYLVANIA

**D**ESPITE the fact that the vast majority of the peptic ulcers which are encountered clinically are located not in the stomach but in the first part of the duodenum, practically all of the work dealing with the role of the acid factor in ulcer has been concerned with the acidity in the stomach. The acidity of the gastric chyme has been assumed to be the important determinant of the acidity of the duodenal contents, and changes in gastric acidity have been considered to be reflected in parallel changes in duodenal acidity. In order to evaluate properly the acid factor in duodenal ulcer it is essential to know something about the acidity and the neutralizing ability at the site of the ulcer and the relationship which exists between the acidity at this site and that present at the same moment in the stomach. Yet little knowledge regarding the actual trend of events in the important "ulcer-bearing" duodenal bulb is available. Kearney (15), studying a group of seven normal persons, found a rough parallelism between the degree of gastric secre-

tory activity and the acidity of the duodenal contents as expressed in pH values. In thirteen patients with duodenal ulcer he was unable to demonstrate this parallelism. Other investigators (10, 11, 17, 18, 19), using men as subjects, have commented on a lack of relationship between gastric and duodenal acidity.

The contents of the first part of the duodenum in the normal dog have been shown to possess a remarkably efficient neutralizing, buffering and diluting capacity following an Ewald meal (2) or a meal of raw meat (23.) The question arose as to whether the neutralizing ability would remain as efficient if the acidity and volume of the gastric contents were to be increased, thereby producing a situation comparable to that found in most patients with duodenal ulcer (1, 4, 5, 6, 7, 8, 9, 12, 13, 14, 20, 21, 22, 24, 25.) The present study was undertaken to get some answer to this question.

We attempted to produce in normal dogs a temporary gastric hypersecretion through the use of potent gastric secretory stimuli, while at the same time recording the changes in acidity which occurred in the pars pylorica and in the duodenal bulb. By comparing these changes with those observed in the same dogs when less potent stimuli were employed, we were able to evaluate the effect of gastric hyperchlorhydria on

\*From the Departments of Physiology and Medicine of The Jefferson Medical College of Philadelphia.

†Aided by a Grant from John Wyeth & Bro., Inc.

‡Ross V. Patterson Fellow in Gastro-Enterology.

Portion of Thesis submitted by Dr. Berk to the Faculty of the Graduate School of Medicine of the University of Pennsylvania in partial fulfillment of the requirements for the Degree of Doctor of Medical Science (D. Sc.) (Med.) for graduate work in internal medicine.

Submitted January 25, 1942.



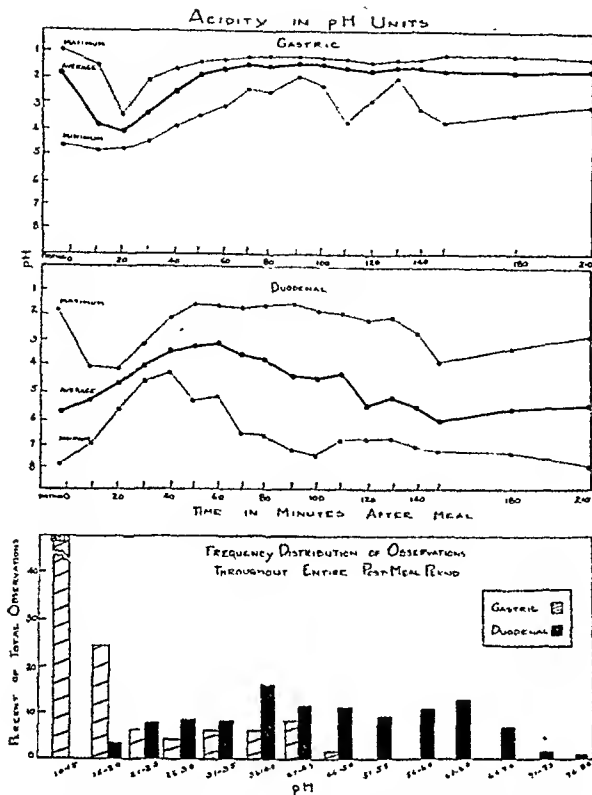


Fig. 1. Acidity in pH units of samples collected simultaneously from just above and just below the pylorus.

the reaction and the neutralizing ability of the first part of the duodenum. The results, we hoped, would help decide whether the acidity in the duodenal bulb is necessarily a reflection of that in the stomach.

#### METHOD

Dogs were prepared with cannulated gastric and duodenal fistulas and were then trained and maintained in the manner described in a previous paper (2.) Fractional samples were removed simultaneously from the gastric and duodenal segments at ten-minute intervals for a half hour in the fasting state and for two and a half hours after the beginning of the meal and at half-hour intervals for an additional hour. The pH of each specimen was immediately determined by means of a Leeds and Northrup pH indicator, which uses a glass electrode. After filtration, the free and total acidity of each specimen was estimated, using Toepfer's reagent and phenolphthalein as the respective color indicators. On each duodenal specimen, in addition, there was determined what was called the excess neutralizing ability (2, 3.) This consisted of the amount of tenth normal hydrochloric acid necessary to lower the pH to the point at which Toepfer's reagent indicated a positive reaction for free (3) acid.

For the purpose of approaching maximal stimulation of gastric secretion, histamine and Liebig's meat extract solution (16, 26) were employed together. The beef extract solution (Difco Laboratory paste preparation dissolved in distilled water) was given in 500 cc. quantities by mouth. In a few instances part of the solution had to be introduced through the gastric instillation tube because of the refusal of the dogs to drink all of it. Histamine hydro-

chloride (1:10,000 solution) was then injected subcutaneously in amounts equivalent to 0.1 mg. of histamine base per 10 Kg. of body weight.

Twenty-two experiments were performed on five dogs. In all 2880 different observations were made consisting of 792 determinations of pH, 835 measurements of free acid, 833 measurements of total acidity and 420 measurements of neutralizing ability of the duodenal contents. In expressing the results the four specimens collected in the fasting state were averaged to obtain a single fasting value.

#### RESULTS

##### Acidity in pH units

*Stomach.* The results with histamine and Liebig's extract differed from those obtained following an Ewald meal in that during the early post-meal period the average gastric pH values tended to be higher and the average duodenal values lower so that between twenty and forty minutes after the meal they closely approached each other. On the gastric side this was probably due to the greater diluting and buffering effect of the large bulk of liquid in the stomach at the time.

*Duodenum.* The maximal average hydrogen ion concentration in the duodenal bulb during the period when the stomach content was large was definitely more than it was at any time after the Ewald meal. Not only was the average pH lower, but of all the duodenal post-meal samples, 26.5 per cent had a pH below the critical value of 3.5 which we had adopted for free acid (3) in contrast to the 16.4 per cent with a similar pH following an Ewald meal. Furthermore, a pH of

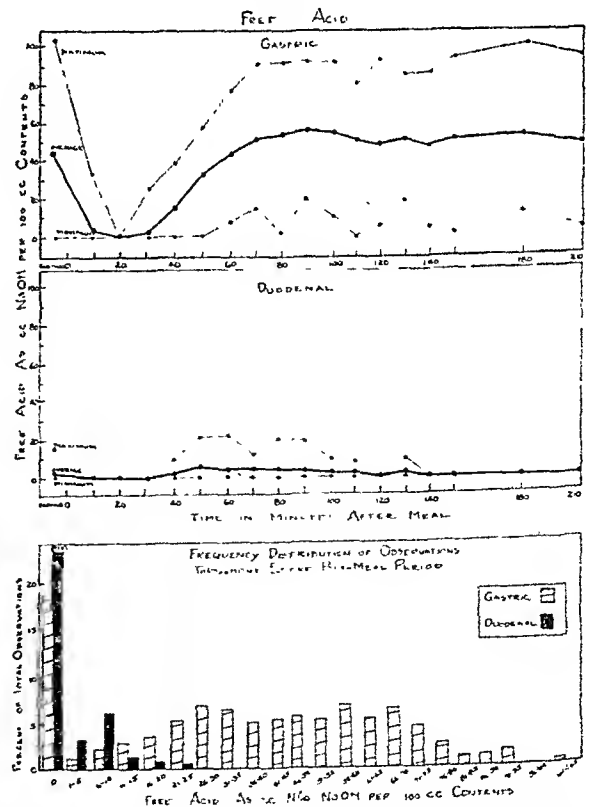


Fig. 2. Free acid as determined on samples collected simultaneously from just above and just below the pylorus.

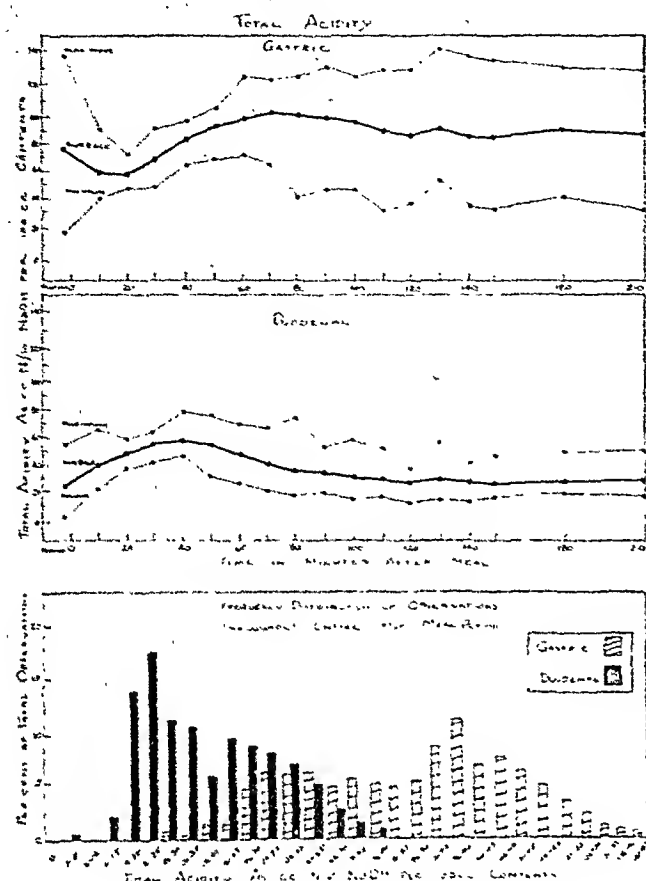


Fig. 3. Total acidity of samples collected simultaneously from just above and just below the pylorus.

less than 3.5 was observed in four or more consecutive samples in half the experiments. With the bread and water meal, on the other hand, pH values indicating hydrogen ion concentrations of this magnitude were met with much more sporadically.

The discrepancy between the lines representing the plotted values of gastric and duodenal pH as shown in Fig. 1 is noteworthy. The lack of parallelism between them indicates the absence of a constant relationship between the acidity simultaneously determined in the stomach and duodenal contents.

#### Free acid

**Stomach.** The average peak values for titratable gastric free acid were essentially the same after the stimuli employed in this study and after the Ewald meal (approximately 55 clinical units.) In contrast to the findings with the bread and water meal, however, the gastric free acid after Liebig's extract and histamine rose much more rapidly.

It will be noted on comparing Figs. 1 and 2 that the curve of average gastric free acid was very different from that of the average duodenal pH. This titration index of gastric acidity cannot be relied on, therefore, to give any idea of the coexistent effective acidity in terms of pH to be found in the duodenal bulb.

**Duodenum.** With the stimulus used by us, the average free acid values found in the first part of the duodenum were definitely higher than they were after the Ewald meal. Of the 328 samples obtained after stimulation with histamine and meat extract, forty-three or 13.1 per cent were positive for free acid with Toepfer's reagent. We have demonstrated that dilution of the filtered duodenal samples preparatory to

titration results in a number of false negative free acid readings (3.) Since our end point with Toepfer's reagent was in the neighborhood of pH 3.5, it must be assumed that all specimens with a pH of 3.5 or less in the unfiltered and undiluted state contain free acid. After qualifying our figures to allow for this error 26.5 per cent of our samples may be considered as positive for free acid. This represents an increase of 61.5 per cent over similar findings with the Ewald meal.

#### Total acidity

**Stomach.** With the stimuli we used, both the average level and the peak value for total acidity in the pars pylorica were slightly less, surprisingly, than those obtained subsequent to the Ewald meal. As has been noted in the case of gastric free acid, total acidity concentrations rose more rapidly than after the bread and water stimulus.

As in the case of free acid, the average gastric total acidity curve was of an entirely different character from that of the curve of average duodenal pH (Fig. 1.) Hence, this measure of stomach acidity is equally unreliable as an index of the behavior of the effective acidity (pH) existing in the duodenal bulb over the same period of time.

**Duodenum.** In the duodenal bulb there was a more or less precipitous rise in the titratable total acidity. During the first forty minutes of the period following the giving of histamine and meat extract, the total acidity values were approximately double those present following the Ewald meal. After that they declined to values about equal to those obtained with the Ewald meal. There was less difference between the values for total gastric and total duodenal acidity at the peak of secretion following stimulation by histamine and meat extract.

The curve of values for average duodenal total acidity was, at best, only roughly similar to that of average gastric total acidity. Between forty and a hundred minutes after the stimulus these curves were actually divergent. This shows again the lack of close relationship between the acidity of the gastric con-

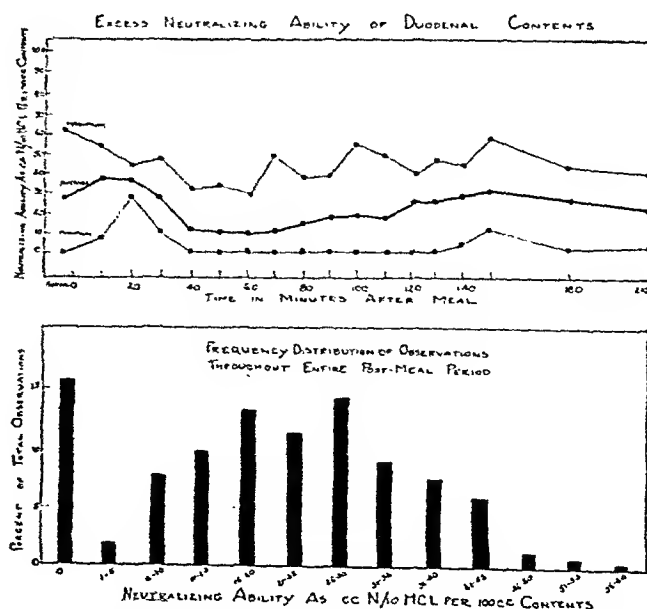


Fig. 4. Excess neutralizing ability of the contents of the first part of duodenum.

tents and that of the contents of the first part of the duodenum.

#### *Excess neutralizing ability of the duodenal contents*

The excess neutralizing ability of the contents of the first part of the duodenum is a measure of the reserve capacity which these contents possess to neutralize, buffer and dilute the chyme received from the stomach above that necessary to offset the free acid content (2, 3.) Of the samples obtained after stimulation 13.8 per cent showed no excess neutralizing ability, and the range of values in terms of clinical units was from 0 to 60. Only 2.7 per cent of the post-Ewald meal samples showed no excess neutralizing ability, and the range of values was from 0 to 100.

### DISCUSSION

A surprising finding was the failure of both the gastric hydrogen ion concentration and titratable acidity, after the use of such potent secretagogues as histamine and Liebig's extract, to reach peak values higher than those obtained with bread and water stimulation. This would suggest the presence of some regulatory mechanism, but other factors undoubtedly played a part. The buffering action of the beef extract solution is considerable, and its presence enhanced the neutralizing power of the stomach. The more rapid emptying due to the liquid state of the meal doubtless removed a large amount of acid from the stomach. Finally, it must be remembered that the titratable acidity values indicate concentration of acid in the total gastric contents and give no idea of the volume of secretion. Despite the similarities between the values for titratable acidity following the two test meals, there is reason to believe that the volume of secretion following Liebig's extract and histamine was much greater than that after the Ewald meal.

The sharp increase in hydrogen ion concentration and free and total acidity in the duodenal bulb during the early post-meal period was probably not caused by gastric hypersecretion alone. Because the Liebig's extract meal is able to leave the stomach rapidly, there results an invasion of the duodenal bulb by large quantities of acid chyme. Evidence that the gastric discharge was rapid and profuse was seen in the large amount of duodenal contents obtained and the ease with which they could be collected, in contrast to our experience with other test substances. Doubtless an additional factor was the buffering action of the solution of meat extract. Once the stomach contents have achieved a high degree of acidity, the protein buffers act to maintain that acidity and render its neutralization more difficult.

Despite the action of these several factors, it is notable that the lowest average pH achieved in the first part of the duodenum was 3.11, which is just below the end point for free acid. Moreover, inadequate neutralization (failure to neutralize free acid as

evidenced by inability to maintain a pH of 3.5 or above) was shown in the average figures for the samples observed only at forty, fifty and sixty minutes after the meal. When the experiments are analyzed individually, duodenal neutralization is seen to be more impaired than the average values had suggested. As noted in the results, in half the experiments, four or more consecutive post-meal duodenal samples had a pH of 3.5 or less.

It can be concluded, therefore, that gastric hypersecretion combined with rapid stomach emptying and buffer interference frequently renders duodenal neutralization inadequate in the normal dog. Generally the inadequacy is slight and effective neutralization is rapidly restored. In some instances, however, the neutralizing, buffering and diluting capacity of the contents of the duodenal bulb may be insufficient for considerable periods of time.

As compared with the findings after the Ewald meal, the higher duodenal acidity, despite the same or even a lower gastric acidity is indicative of a lack of absolute correlation between the acidities in terms of concentration in these parts. The tendency for the pH and the total acidity values in the duodenal bulb to exhibit no close relationship to similar values simultaneously determined in the pars pylorica is still further evidence of an independency of reaction in these contiguous regions. This feature was noted by us before in normal dogs who had been fed a carbohydrate-water meal (2.)

### SUMMARY AND CONCLUSIONS

1. An attempt was made to produce temporary gastric hypersecretion in normal dogs by the simultaneous action of histamine and Liebig's extract for the purpose of observing its effects on duodenal bulb reaction and neutralizing ability.

2. During the early post-meal period there was a more or less precipitous increase in acidity in the duodenal bulb and more than the usual volume of duodenal contents, indicating the occurrence of both gastric hypersecretion and rapid emptying of the stomach.

3. Gastric hypersecretion and rapid stomach emptying frequently interfere with adequate neutralization in the duodenal bulb. The impairment is usually slight and is rapidly corrected, but in some instances neutralization may be inadequate for considerable periods of time.

4. There is no good correlation between the degree of gastric acidity and the reaction and neutralizing ability of the contents of the first part of the duodenum.

5. None of the customary measures of acidity in the stomach can be relied on to indicate the behavior of the corresponding effective acidity (pH) in the first part of the duodenum.

### REFERENCES

1. Alvarez, W. C.: Standards of Normal in Gastric Secretion. *Ann. Int. Med.*, 6:315, 1932.
2. Berk, J. E., Thomas, J. E. and Rehfuess, M. D.: The Reaction and Neutralizing Ability of the Contents of the Pyloric Antrum and First Part of the Duodenum in Normal Dogs Following an Ewald Meal. *Am. J. Physiol.* In press.
3. Berk, J. E., Thomas, J. E. and Rehfuess, M. E.: Limitations in the Use of Color Indicators in Gastric Analysis. *Am. J. Dig. Dis.* In press.
4. Bloomfield, A. L.: Clinical Aspects of Gastric Secretion. *Ann. Int. Med.*, 6:307, 1932.
- Idem: The Problems of Gastric Hyperacidity. *Am. J. Dig. Dis.*, 6:700, 1939.
5. Bloomfield, A. L. and Pollard, W. S.: The Diagnostic Value of Studies of Gastric Secretion. *J. A. M. A.*, 92:1508, 1929.
6. Bloomfield, A. L., Chen, C. K. and French, L. R.: Basal Gastric Secretion as a Clinical Test of Gastric Function with Special Reference to Peptic Ulcer. *J. Clin. Invest.*, 19:863, 1940.
7. Bockus, H. L., Glassmire, C. and Bank, J.: Fractional Gastric Analysis in 200 Cases of Duodenal Ulcer. *Am. J. Surg.*, 12:6, 1931.
8. Cheney, G. and Bloomfield, A. L.: Gastric Function in Cases of Gastric and Duodenal Ulcer. *J. Clin. Invest.*, 5:511, 1928.
9. Comfort, M. W. and Osterberg, A. E.: Gastric Secretion After Stimulation with Histamine in the Presence of Various Types of Gastric and Duodenal Lesions. *J. A. M. A.*, 97:1141, 1931.

10. Einhorn, M.: The Fractional Examination of the Duodenal Contents. *Am. J. Med. Sci.*, 156:817, 1918.
- Ibid: Fractional Examination of the Duodenal Contents in Peptic Ulcer. *J. A. M. A.*, 77:1471, 1921.
- Ibid: The Duodenal Tube and Its Possibilities. F. A. Davis, Philadelphia, 1926.
11. Friedenwald, J. and Sindler, J.: Fractional Analysis of the Duodenal Contents in Normal Individuals. *J. A. M. A.*, 77:1469, 1921.
12. Hurst, A. F.: Hypersthenic Gastric Diathesis. *Lancet*, 2:1369, 1922.
13. Hurst, A. F. and Stewart, M. J.: Gastric and Duodenal Ulcer. Oxford University Press, London, 1929.
14. Hurst, A. F. and Venables, J. F.: The True Incidence of Hyperchlorhydria in Gastric and Duodenal Ulcer. *Guy's Hosp. Reports*, 79:249, 1929.
15. Kearney, R. W., Comfort, W. W. and Osterberg, A. E.: Hydrogen Ion Concentration of the Duodenal Contents Under Fasting Conditions in Normal Persons and in Patients with Duodenal Ulcer: A Comparative Study. *J. Clin. Invest.*, 20:221, 1941.
16. Lattimore, J. D., Gold, A. and Ebendorf, H. C.: The Wilhelmj Test Meal. *Am. J. Clin. Path.*, Tech. Supp., 4:24, 1940.
17. McClure, C. W., Wetmore, A. S. and Reynolds, S.: Physical Characters and Enzymatic Activities of Duodenal Contents: Findings During Gastric Digestion in Normal Young Men. *J. A. M. A.*, 77:1468, 1921.
18. McClure, C. W. and Wetmore, A. S.: Studies in Pancreatic Function Enzyme Concentration of Duodenal Contents After the Ingestion of Pure Foodstuffs and Food Mixtures by Normal Men. *Boston M. and S. J.*, 187:882, 1922.
19. Okada, S. and Arai, M.: The Hydrogen Ion Concentration of the Intestinal Contents. *J. Biol. Chem.*, 51:135, 1922.
20. Pollard, W. S.: Histamine Test Meals. An Analysis of 988 Consecutive Tests. *Arch. Int. Med.*, 51:903, 1933.
21. Rehfuess, M. E.: Possibility of Fractional Gastric Analysis. *J. A. M. A.*, 71:1534, 1918.
- Ibid: Diagnosis and Treatment of Diseases of the Stomach. W. B. Saunders, Philadelphia, 1927.
22. Ruffin, J. M. and Dick, M.: The Significance of Gastric Acidity After Histamine Stimulation. A Statistical Study of 2377 Gastric Analyses. *Ann. Int. Med.*, 12:1940, 1939.
23. Thomas, J. E.: Maximal Acidity of the Intestinal Contents During Digestion. *Am. J. Dig. Dis.*, 7:195, 1940.
24. Vanzant, F. R., Osterberg, A. E., Alvarez, W. C. and Rivers, A. B.: Studies of Gastric Pepsin. II. Secretion of Pepsin in Cases of Duodenal Ulcer and Pseudo-Ulcer. *J. Clin. Invest.*, 12:557, 1933.
25. Vanzant, F. R., Alvarez, W. C., Berkson, J. and Eusterman, G. B.: Changes in Gastric Acidity in Peptic Ulcer, Cholecystitis and Other Diseases Analyzed with the Help of a New and Accurate Technique. *Arch. Int. Med.*, 52:616, 1933.
26. Wilhelmj, C. H., O'Brien, F. T. and Hill, F. C.: An Improved Gastric Test Meal. *Am. J. Dig. Dis.*, 3:319, 1936.

## Impending Gangrene of the Foot Following Treatment for Pruritus of Jaundice with Ergotamine Tartrate: Report of Case

By

LUCIAN A. SMITH, M.D.\*

and

GEORGE B. EUSTERMAN, M.D.†

ROCHESTER, MINNESOTA

ERGOTAMINE tartrate is used extensively at present for treatment of migraine. Many physicians fear the effect of the drug and some even prohibit their patients from using it. The impression of many others, however, who have used it extensively in cases of migraine is that it is safe even when used several times a week. Rarely is there any disturbance, and, so far as we know, no serious results have been reported from this type of administration. There is danger, however, when ergotamine tartrate is used in larger quantities to relieve the itching of jaundice. The cases reported by Comfort and Erickson (1) illustrated such dangers. It is possible that patients who have adverse reactions have an idiosyncrasy to the drug and that the presence of a damaged liver may be a factor in producing this idiosyncrasy.

It is well to study the danger of using ergotamine tartrate in jaundice because in many cases in which the patient is nearly frantic with itching it is the only drug that may give relief. It seems worth while to report another case of ergotism resulting from its use. Additional observations made in this case suggest that the administration of ergotamine tartrate may have added to the damage already incurred to the liver as a result of biliary retention.

### REPORT OF CASE

The patient, a married woman twenty-nine years of age, registered at the Mayo Clinic July 23, 1939. She complained of jaundice of five weeks' duration accompanied by intense itching. In September, 1938, two days after she had given birth to a child, she had had an attack of gall stone colic. After several more attacks the gall bladder had been removed on February 24, 1939. The

surgeon had found subacute cholecystitis with many stones. On the twenty-first post-operative day, left femoral thrombophlebitis had developed and on the following day symptoms suggestive of a left basal pulmonary infarct had been present. On June 15, 1939, itching appeared, followed in one or two weeks by epigastric pain and jaundice.

Examination at the clinic revealed a thin, somewhat nervous woman who had deep jaundice. Her skin was badly excoriated by her fingernails. The liver was firm, rounded and tender; its edge was 3 cm. below the right costal margin and 5 cm. below the xiphoid process. Mild edema of the left leg was present. Pulsations were normal in all peripheral arteries.

A tentative diagnosis of obstructive jaundice owing to stone in the common bile duct or stricture of the duct was made. Because of the necessity of relieving the intense itching, ergotamine tartrate was given hypodermically, together with barbiturates. Fair relief of itching was obtained with administration of one ampule (1.0 cc. containing 0.5 mg.) of ergotamine tartrate. This dose was given once a day from July 23 to July 27, 1939, inclusive. The total amount given was 2.5 mg. in five days. On July 25 and 26, colicky epigastric pain developed, together with an elevation of the quantity of serum bilirubin from 9.1 to 21.4 mg. per 100 cc., and an increase of itching. On July 28 the patient seemed weak and almost comatose. This sleepiness seemed deeper than we felt could be explained by the amount of barbiturates which had been given. The use of ergotamine tartrate and of the sedatives was discontinued on July 28; the next day the drowsiness disappeared and her general condition seemed improved. The value for serum bilirubin was still elevated. The itching increased and became almost uncontrollable. On July 29 and 30 she was given 3.25 mg. of ergotamine. On July 31, at 2 a.m. she was awakened by pain, throbbing and a frozen sensation in the right foot; by morning the foot felt numb and burned. Because of a misunderstood order, 0.5 mg. of ergotamine tartrate and 1½ grains (0.1 gm.) of seconal (sodium propylmethylcarbonylallylbarbiturate)

\*Fellow in Medicine, Mayo Foundation.  
†Division of Medicine, Mayo Clinic.  
Submitted March 2, 1942.

were administered at 2:00 a.m. and the dose of ergotamine tartrate was repeated at 8:30 a.m. which meant that a total of 6.75 mg. had been given in a period of nine days.

When the patient was seen at 9:00 a.m. on July 31, 1939, severe ischemic pain had developed in the right foot and extended up to both malleoli. A bluish pallor was present in the affected part and there was a distinct lowering of the temperature of the skin of the extremities, especially of the right foot. Pulsations could not be felt in the popliteal, posterior tibial or dorsalis pedis arteries of both legs, and it was difficult to detect any pulsation in the radial and ulnar arteries. Pulsations could be felt easily in the temporal arteries. Although pulsations of the brachial arteries were present, the blood pressure could not be determined. When the feet were in the dependent position, rubor was absent.

A diagnosis was made of ergotism. Arterial occlusion in the right leg was suspected. At 9:30 a.m.,  $\frac{1}{2}$  grain (0.032 gm.) of papaverine hydrochloride was given intravenously. The arterial pulsations did not change quickly, but it was possible to obtain blood pressure readings of 106 systolic and 70 diastolic, measured in millimeters of mercury, about ten minutes later. The right extremity was wrapped in blankets and a baker was placed over the trunk. At 3:30 p.m., because ischemic pain continued, the patient was transferred to an oscillating bed in a room in which the temperature was kept constant at 86° F. and in which the humidity was 40 per cent. Medication consisting of  $\frac{1}{6}$  grain (0.01 gm.) of morphine sulfate was given with 1 ounce (30 cc.) of alcohol by mouth. By 8:00 p.m. the ischemic pain was still as severe, but when present it came at longer intervals. The temperature of the skin of the right foot had increased so that it was only 2 or 3° C. less than that of the left.

With the use of vasodilating measures the itching increased to an intolerable point, but the administration of barbiturates, morphine or codeine and histaminase in a dosage of four capsules five times daily eventually controlled it. By the afternoon of August 1 the condition of the right foot was much better and all the other extremities appeared to be normal. Dependency of the right foot was followed by fairly prompt reddening and venous dilatation. On August 2, 1939, the right foot was warm and vasodilatation seemed complete. On August 3 subungual blebs appeared at the tips of the toes. There was a redness beneath the previously ischemic region and old scratch marks on the right foot were somewhat infected. Slight edema of the foot was present. The patient was removed from the warm room and the infection was combated successfully by wet dressings and immobilization and elevation of the foot. Because of a slight residual weakness of dorsiflexion of the right foot and a slight diminution of sensation to pin pricks over its dorsum, a protecting cradle and a light, right angle, foot splint were used to prevent foot drop.

During these difficulties, the patient's general condition was serious. The value for serum bilirubin increased from 9.1 to 21.4 mg. in two days. Coincident with the onset of the symptoms of ergotism in the extremities, she had fever for five days, with signs of toxicity and a more rapid pulse than would be expected with the height of the fever. The pulse rate was between 100 and 140 beats per minute for six days ending August 6. The value for serum bilirubin rose to a maximum of 37.5 mg. on August 2, only to decrease as the symptoms of ergotism in the leg disappeared. Supportive measures for the liver were used throughout the stay in the hospital.

At operation on August 12, 1939, a stricture of the common bile duct and an enlarged liver were revealed. Anastomosis was made between the hepatic ducts and the distal portion of the common bile duct. The patient left the hospital much improved.

On examination in April, 1940, there was no noticeable abnormality in the appearance of the feet, dorsiflexion of

the right foot was not weakened and the only sensory abnormality was slight paresthesia.

## COMMENT

Lewis (2) found that in fowls the injection of ergotoxine did not stop the circulation, but, by producing spasm, slowed the blood stream to such an extent that changes appeared in the blood vessels with thrombi, proliferation and hyaline degeneration of the endothelium. Such changes were apparent in Yater and Cahill's (3) case, as demonstrated arteriographically and pathologically. In that case the leg was amputated.

The findings at necropsy in the case of Gould and his associates (4) indicated that although the changes in the peripheral vascular system were the most profound, the walls of the arterioles of the pancreas, kidney and liver were thickened, "being about half the diameter of the lumens." These authors did not state whether necrosis of the hepatic parenchyma, involving principally the central portion of the lobules, seemed related at all to the vascular changes.

We cannot state that the administration of ergotamine tartrate in the case we have reported was responsible for the sudden change for the worse in function of the liver, although we suspect that it was. The fact that drowsiness and the rise in the value for serum bilirubin were present after administration of ergotamine tartrate disposes us to feel that the drug may have injured the liver. Furthermore, when the use of ergotamine tartrate was interrupted for a day the patient's condition improved and when it was given again the difficulties recurred. On searching the literature, however, we could not find any conclusive evidence that ergotamine is toxic to the liver. Variable degrees of jaundice were reported by Kobert (5) and Davidson (6) in fatal cases in which pregnant women took varying amounts of preparations of ergot to produce abortion. It is possible that, since in these cases there were hemorrhages in other organs of the body, the jaundice may have been the result of absorption of extravasated blood. Nevertheless, there is a possibility that ergotamine tartrate can injure the liver.

The dose used in this case has been used many times at the Mayo Clinic without causing adverse reactions. Hence, we feel that this woman must have had some sensitiveness to the drug which predisposed her to injury. In cases previously reported, symptoms of toxicity appeared after doses of from 0.5 to 24.0 mg. given hypodermically. When the drug was given orally, the range of dosage in those cases in which such symptoms appeared was from 10.0 to 60.0 mg.

## SUMMARY

Ergotamine tartrate in treatment of the itching of jaundice must be used with care. Patients may have an idiosyncrasy for the drug or a cumulative reaction may develop. The case of a woman who had severe jaundice and who was given 6.75 mg. of ergotamine tartrate in nine days is reported. Signs of impending gangrene developed in one foot. Fortunately, the prompt use of measures designed to produce vasodilatation led to recovery and saving of the foot. Certain observations suggested that administration of ergotamine tartrate wrought further injury to a liver already damaged by jaundice.

## REFERENCES

1. Comfort, M. W. and Erickson, C. W.: Untoward Effects from the Use of Ergot and Ergotamine Tartrate. *Ann. Int. Med.*, 13:46-60, July, 1939.
2. Lewis, Thomas: The Manner in Which Necrosis Arises in the Fowl's Comb Under Ergot Poisoning. *Clin. Sci.*, 2:43-55, Sept., 1935.
3. Yater, W. M. and Cahill, J. A.: Bilateral Gangrene of Feet Due to Ergotamine Tartrate Used for Pruritus of Jaundice; Report of a Case Studied Arteriographically and Pathologically. *J. A. M. A.*, 106:1625-1631, May 9, 1936.
4. Gould, S. E., Price, A. E. and Ginsberg, H. I.: Gangrene and Death Following Ergotamine Tartrate (Gynergen) Therapy. *J. A. M. A.*, 106:1631-1635, May 9, 1936.
5. Robert, R.: Ueber die Bestandtheile und Wirkungen des Mutterkorns. *Arch. f. exper. Path. u. Pharmacol.*, 18:316-350, 1884.
6. Davidson, A.: Fatal Case of Poisoning by Ergot of Rye. *Lancet*, 2:526-527, Sept. 30, 1882.

## Contributions Made to Knowledge in Regard to the Pancreas in 1941

By

R. ELMAN, M.D.

and

A. M. LARGE, M.D.

ST. LOUIS, MISSOURI

THE war has prevented review of many foreign papers which are not available, and has, doubtless, diminished interest in diseases of the pancreas. Nevertheless, considerable advance has been made in 1941, particularly in the diagnosis and surgical treatment of carcinoma of the head of the pancreas. As in previous reviews (10, 11, 12), only papers containing objective data which seemed significant to the reviewers, were selected for discussion; none dealing with the islet tissue of the pancreas was included.

### PANCREATIC INSUFFICIENCY

A variety of interesting observations, both clinical and experimental, have been made, particularly in regard to the diagnosis of decreased or absent function of the external secretion of the pancreas. Using the secretin stimulus and a double-lumened tube, as described in previous reviews, Diamond and Siegel (9) described 116 further observations on 90 humans, 24 of them normal. In carefully controlled observations on three normal subjects, Comfort and Osterberg (7), using the same technic, studied the effect of various stimuli on pancreatic secretion and found that the combined use of mecholyl and secretin is superior to any other stimulants or to each of these drugs alone, particularly in that the bicarbonate value is higher and the enzyme concentration is increased two to five times. In 40 minutes a volume of nearly 150 cc. was obtained. Gulzow (20) used various pancreatic stimulants in dogs and found a rise in blood amylase followed the injection of pilocarpine, histamine and acetylcholine, whereas after pancreatectomy no rise occurred. Atropine also seemed to prevent the rise induced by pilocarpine and acetylcholine in the normal dog. On the basis of these observations it might be of interest to study variations in pancreatic ferments in the blood following the use of the secretin test in humans, i.e., a rise might thus indicate a normal pancreas, a flat curve pancreatic insufficiency.

Clinically, pancreatic insufficiency is often diagnosed as pancreatic achylia. Beazell, Schmidt and Ivy (2) have presented considerable data on four such patients, all exhibiting frequent bulky stools and loss of weight. They all showed absence of pancreatic ferments in fluid obtained by simple duodenal drainage and con-

siderable steatorrhea and creatorrhea after a standard diet. Treatment consisted of the ingestion of an initial dose of raw pancreas or of pancreatin of 24 grams a day (equivalent to 240 cc. of pancreatic juice) given in eight gram enteric-coated capsules three times a day; it was effective in that the stool bulk was reduced in 24 hours and gain in weight of six to forty pounds in two and one-half to thirty-six months occurred. The steatorrhea was reduced two-thirds as was the creatorrhea, though 12 to 28 per cent of the nitrogen was still lost in the stool. Whipple and Baumann (59) studied four cases in which no pancreatic juice was reaching the duodenum following pancreatic resection for carcinoma; in three of them fat absorption was normal, indicating that under certain circumstances pancreatic insufficiency can be completely and spontaneously compensated. Jeffery (24) described a case of cystic fibrosis of the pancreas in an infant dying at five and one-half months after a history of failure to gain, and persistent paroxysmal cough. This child had normal stools, and showed absence of metaplasia in the lungs and but slight fatty infiltration of the liver; these findings were considered unusual in a case of cystic fibrosis.

### THE PANCREAS AND THE FATTY LIVER

The role of the pancreas in metabolism of fat formed the subject of an extensive experimental study by Montgomery (37) who has reported a great deal of data on 27 dogs, 19 subjected to duct ligation and eight depancreatized. From his findings it seems clear that the external secretion of the pancreas is the essential factor in the control of lipid metabolism, inasmuch as the lipid changes in the blood and liver of duct-ligated dogs are comparable to those in depancreatized dogs maintained with insulin, and that unactivated pancreatic juice controls these changes the same as raw pancreas. Evidence of the same sort is furnished by Entenman, Chaikoff and Montgomery (14) and by Montgomery, Entenman and Chaikoff (38.) In the former paper, the blood lipid changes were studied in depancreatized and duct-ligated dogs and pancreatic juice found to be active in raising the hypolipemia produced by these procedures. In the second paper daily feeding of pancreatic juice had the effect of preventing fatty livers as compared with control dogs. After this apparent clarification, the same



authors (Entenman and Chaikoff) (13) report further experiments in 25 depancreatized dogs carefully prepared and maintained with insulin, in whom an average dose of choline of 36 mg. per kilo per day, prevented fatty livers, yet a total daily dose of one gm. of pancreatic extract containing but 13 mg. of choline also prevented fatty livers. The activity of the pancreatic extract was heat-labile because after heating it was inactive even when the dose was increased four times. In the increasing maze of conflicting data regarding the lipotropic factor in the pancreas, the suggestion made last year might, perhaps, be repeated; i.e., that lipocaic though present in the pancreas, is an enzyme (or vitamin) which is normally absorbed in food with the aid of pancreatic juice, just as Vitamin K, though present in the liver, is absorbed with the aid of bile. Of course, it is undoubtedly true that there are many types of fatty livers (as pointed out by Longenecker, Gavin and McHenry) (33) each of which responds to different lipotropic agents. These workers have extended their observations on the fatty liver in rats fed a diet containing a potent liver extract, to fat synthesis in the entire body particularly as affected by various vitamins of the B complex. Shapiro and Wertheimer (49) confirmed the earlier work of McHenry and his co-workers, that diet-induced fatty livers in rats are influenced by pancreatic extracts (lipocaic) but not by choline, and that the active principle is heat labile and is not present in other tissues. In cats, Sproul and Sanders (53) found no change in the liver lipids following pancreatic duct ligation or partial or complete pancreatectomy (curiously, however, the normal cat apparently has a high liver fat; i.e., 12 to 19 per cent.) They did find that the fat content of the stool was increased four to six times the normal in their experiments, and that the Vitamin K content of the liver fell especially following pancreatectomy. Though the results were variable, the prothrombin time was increased in all experiments, especially following pancreatectomy.

The clinical relation of fatty liver to pancreatic disease was emphasized by Schnedorf and Orr (50), who found fatty livers at autopsy in eight of 35 cases of cancer of the pancreas and two of 17 cases of cancer of the ampulla of Vater. A contrasting experience is that of Whipple (60) who found no fatty livers in his cases coming to autopsy in which a two-stage operation for excision had been done.

#### CARCINOMA OF THE PANCREAS

An unusually large volume of literature has developed in the past year, not only from the diagnostic, but particularly from the therapeutic (surgical) point of view.

Of the diagnostic papers that of Berk (3) is the most interesting. Besides his own 35 cases, he has gathered much data from the literature and has polled 120 physicians in regard to the diagnostic features of this disease. This study should dispel the commonly held idea that painless jaundice is a diagnostic feature in carcinoma of the pancreas. Thus, he found that whereas but 2.5% of the medical men considered pain of diagnostic value, 76% of the patients presented this symptom; on the other hand, 92 per cent of the physicians put jaundice as the most important first sign, whereas, only 63 per cent of the proved cases had jaundice as the initial manifestation. To emphasize

still more the infrequency of really painless jaundice in carcinoma of the pancreas, only 17 per cent of 68 reported cases presented this manifestation at the onset and in only 13 per cent of 217 cases is it mentioned at any time during the disease. Fatigue, weakness, anorexia, nausea and vomiting, each averaged about 40 to 50 per cent; diarrhea, contrary to the experience of many, appeared in only 10 per cent of the cases. On physical examination, the importance of the enlarged liver is indicated by its detection in 63 per cent (in some series, as high as 80 per cent) of cases. The distended gall bladder was found in 87 per cent of 175 jaundiced cases at operation or autopsy, thus verifying Courvoisier's law. That this finding is not so easy to detect at the bedside is indicated by its observation in only 50 per cent of cases (a figure which to the present reviewers is much too high.) Ascites before operation was mentioned in only 15 per cent of all cases, though of those coming to operation or autopsy, 30 per cent exhibited some fluid. Nearly two-thirds of patients subjected to X-ray examination showed no abnormal findings. Of the other clinical papers Kauer and Glenn (25) reported 38 cases with substantially the same general conclusions. This is also true of the report by Franco (17) who described 40 cases of carcinoma of the head of the pancreas; in 26 of these cases a barium meal X-ray series was done. Abnormalities were found in 16 of them, of which 11 showed only duodenal changes. Forty cases are described by Friedenwald and Morrison (18), the diagnosis in 31 confirmed by operation or autopsy. Of special interest was the study of pancreatic ferments in eight cases, six yielding abnormal findings. Persistent diarrhea as a first symptom was noted in seven cases and bulky stools in nine. Papillary cystadenoma of the pancreas is a rare tumor, but Kennard (26) reported one such case and reviewed the literature; the tumor was excised successfully.

The surgical cure of carcinoma of the pancreas, a dim and unlikely prospect a few years ago, seems on its way toward fulfillment. Two-stage resections were reported by Luke (34), by Moreland and Freeman (39) and by Orr (42), but this operation now seems to be largely replaced by a one-stage procedure which is thus holding the center of the stage. Whipple (60), in a brief report of 41 recently collected cases in which the two-stage operation was done, pointed out that five developed biliary, and eight pancreatic fistula after operation, of which the former seldom close. He described the first successful one-stage radical pancreaticoduodenectomy performed in March, 1940; the patient gained 20 pounds in weight and was well 14 months after operation. Trimble, Parsons and Sherman (57) also reported a successful one-stage operation carried out April 26, 1940; the patient gained 15 pounds in weight, and was well nine months later. These last authors left the gall bladder intact, implanting the dilated common duct into the distal limb of the jejunum just beyond the antecolic gastrojejunal anastomosis. This paper is especially valuable because the operative technic is beautifully illustrated by Max Brodel; though they must have been done not long before his death, the drawings show not the slightest diminution in the perfection for which this medical illustrator was so justly famous. The paper of Hunt

(22) must be included even though he dealt only with carcinoma of the ampulla of Vater, because this neoplasm in general, presents diagnostic and therapeutic problems similar to those of carcinoma of the head of the pancreas. This paper contains an exhaustive review of the literature. Four of his own cases are described; two had local transduodenal resections, both dying of extension of the disease two and three years later. The Whipple one-stage procedure was done in the third case, the patient remaining well one year later. In the fourth case the diagnosis was missed at the first operation; a single stage resection was later successfully carried out though only a month had elapsed since the last operation.

### X-RAY DIAGNOSIS

Several papers have appeared on the value of the X-ray following the ingestion of the barium meal in the diagnosis of pancreatic disease. Feldman (15) described seven cases with specific changes in the duodenum, although there was no confirmation of the lesion by operation or autopsy. Brown, McCarthy and Fine (5) reported 12 cases, emphasizing the importance of films taken in the right lateral position. Ochsner (40) discussed a number of isolated observations made on the radiological effects of various periduodenal and extra duodenal lesions. Flynn (16) presented a case report in which a roentgenological diagnosis was made of obstruction in the second portion of the duodenum; the significance of this finding was apparently missed by the surgeon who at operation merely removed a gall bladder containing stones and did a gastro-enterostomy. Nine months later jaundice developed and operation now showed an obvious carcinoma of the pancreas, confirmed by biopsy. This case is to be added to other experiences mentioned last year and Hunt's fourth case (22) (see above) emphasizing the importance of palpating and, perhaps, visualizing the pancreas carefully during biliary operations, with neoplasm in mind.

### ACUTE PANCREATITIS

Connell (8) reported 26 cases briefly, 22 of which were operated on with a mortality of 36 per cent, whereas four were not operated on, all dying, the lesion being found at autopsy. No differentiation was made between the necrotic and edematous type of pancreatitis, nor were the lesions found at operation described. As mentioned in previous reviews, the fatal cases are probably all instances of acute necrosis rather than simple inflammation of the pancreas. Lewison, (29) described an interesting case of acute pancreatitis falling into the latter group. At operation there was a glassy edema surrounding the pancreas which was enlarged. The gall bladder was removed and a T-tube inserted in the common duct. The serum amylase fell from a high level to normal following operation but rose later only to fall again when the T-tube was removed; the secondary rise was explained as being due to pressure of the long arm of the T-tube in the pancreatic duct. Ogilvie (41) described four cases of acute pancreatitis all coming to autopsy and showing associated duodenal diverticulæ which had evidently caused obstruction at or near the Ampulla of Vater. Loe (32) described an interesting case of acute pancreatitis operated on twice for recurrent attacks of pain, the lesion in the pancreas

being of the interstitial variety. Cholecystectomy, choledochostomy and drainage of the head of the pancreas were done at the second operation with relief of symptoms for three and one-half months.

Experimental pancreatitis was produced by Ireneus (23) in 40 dogs by the injection of the animal's own bile into the accessory pancreatic duct. Progressive microscopic details were described. Several dogs merely developed an edematous lesion and recovered in 10 days to two weeks. The old "common channel" theory was investigated by Schiller (47), this time from the liver side. This observer noted that the liver in six out of 16 cases of acute pancreatitis showed hepatic changes including fatty infiltration. In one patient dying of hemorrhage pancreatitis he found fat necrosis in the liver, which he interpreted as due to reflux of lipase into the biliary tract.

### SERUM AMYLASE

Popper and Sorter (45) studied the rise of the serum amylase after ligation of all pancreatic ducts in four dogs. Of the two that survived, the high value returned to normal in one at 11 days, in the other at 23 days. They found no change in serum lipase. Gulzow (20) found that there was one-fifth or less amylase in the red cells as compared with plasma. He injected 500 mg. of Vitamin C intravenously into a patient with an elevated serum amylase due to pancreatitis, and noted a striking fall from 700 to 200 in 30 minutes, which returned to the high level gradually during four hours. This worker depancreatized four dogs, and noted that the blood amylase fell to one-third of its normal level within 48 hours, but tended to return partially to normal with insulin. Bernhard and Rosen (4) found practically no amylase in human red cells, and no differences between serum and plasma. Mekler (36) studied daily variations in blood and urine amylase in 24 patients with a variety of conditions and found little significant changes. Popper and Plotke (44), in dogs, noted that amylase artificially injected into the blood tends to disappear rapidly.

Rhodes (46) reported extensive serum amylase studies in 35 cases of acute pancreatitis. Of 195 tests, high readings were found only when the clinical picture warranted a diagnosis of acute pancreatitis. These were present mostly during the first 24 hours of the attack. He treated all patients conservatively during the acute state. Lewison (30) also reported observations on the serum amylase in a large number of patients, confirming previous work. He studied 13 patients with mumps and found they had elevations of serum amylase unless the disease was mild. On the other hand, of 720 patients without mumps or disease of the biliary tract or pancreas, 94 per cent had normal values.

### PANCREATIC LITHIASIS

Snell and Comfort (52) summarized their experience with 18 cases; 11 of them had colic. Actual or latent diabetes was present in eight and the same number had fatty diarrhea. They also emphasized episodes of nausea and vomiting not necessarily associated with colic. Roentgen evidence of stone was again mentioned as a characteristic finding. Thompson

(56) reported four cases with diabetes; three were operated on, two of which recovered though the stones were not removed. Smith and Bonis (51) observed three cases among 240 X-ray examinations of the pancreatic area. Poppel and Levy (43) reported three cases, and in reviewing the literature found that 204 cases were mentioned in the literature during the past 270 years; half of these were reported between 1925 and 1938, indicating not the growing frequency of the disease, but its more frequent detection, especially with the aid of the X-ray.

#### EXPERIMENTAL PANCREATIC FISTULA

Among many other findings in unanesthetized dogs, Scott, Collignon and Bugel (48) noted that insulin hypoglycemia increased the flow of pancreatic juice, whereas intravenous glucose inhibited this secretion. Greengard, Stein and Ivy (19) found in urine a thermolabile agent which on incubation inactivated the effect of pancreatic secretin, and found that urine concentrates contained a thermostable anti-secretin. Thomas and Crider (55) stimulated pancreatic secretion in dogs with various protein digests and found that they decreased the volume but increased the nitrogen content of the juice as compared with other stimulants such as secretin. Hug (21), in two experiments, found that sulfanilamide appears in the pancreatic juice at about the same concentration as in the blood. This was confirmed by Taylor and Agren (54) with sulfapyridine, who noted, however, that the concentration in bile was much higher. Barrington (1), in cats, found that secretin stimulated not only

the volume of pancreatic juice, but also the output of zymogen granules, and thus the output of enzymes.

#### MISCELLANEOUS

Liedberg (31) performed cholangiograms in 53 patients during operations on the biliary tract, and in 22 noted that the pancreatic duct was visualized. He quoted others as noting the same finding in 10 to 24 per cent of cases. In eight of his cases, the patients exhibited a transient increase of amylase in the urine after operation. Walters and Cleveland (58) have reviewed 255 operations for lesions of the pancreas, 73 per cent of which were for carcinoma; in these a short circuiting operation was performed. There were ten cases of accessory pancreas. There was one operation on the pancreas for every 25 operations on the gall bladder and ducts. Martin (35) operated on an 11 year-old Hindu boy with abdominal pain and an epigastric mass. He found a multilocular cystic adenoma of the head of the pancreas and aspirated or drained many of the cysts; recovery was uneventful and the patient was well two months later. Krieg (28) found 16 cases in the literature and added one case report of his own to the rare condition of hypertrophic pancreatic tissue producing pyloric obstruction. The aberrant pancreatic tissue was successfully removed; curiously enough, it contained no islet tissue. Koucky, Beck and Todd (27) described five cases of pancreatic cyst which perforated spontaneously, producing severe abdominal signs requiring laparotomy; three died. Chapman (6) described a case of pancreatic cyst upon which he operated three times; a persisting fistula was finally successfully implanted into the jejunum.

#### REFERENCES

- Barrington, E. J. W.: *J. Physiol.*, 100:80, 1941.
- Beazell, J. M., Schmidt, C. R. and Ivy, A. C.: *J. A. M. A.*, 116:2735, June, 1941.
- Berk, J. E.: *Arch. Int. Med.*, 68:525, 1941.
- Bernhard, A. and Rosen, M. J.: *Proc. Soc. Exp. Biol. Med.*, 48:575, 1941.
- Brown, Samuel, McConrthy, J. E. and Fine, Archie: *Radiology*, 36:596, May, 1941.
- Chapman, C. L. G.: *Brit. J. Surg.*, 28:633, April, 1941.
- Comfort, M. W. and Osterberg, A. E.: *Am. J. Dig. Dis.*, 8:337, 1941.
- Connel, F. G.: *Ibid.*, 8:327, 1941.
- Diamond, J. S. and Siegel, S. A.: *N. Y. State J. of Med.*, 41:869, April, 1941.
- Elman, R.: *Am. J. Dig. Dis. and Nutrit.*, 6:233, 1939.
- Elman, R.: *Ibid.*, 7:227, 1940.
- Elman, R. and Suchar, L. A.: *Ibid.*, 8:105, 1941.
- Entenman, C. and Chaikoff, I. L.: *J. of Biol. Chem.*, 138:477, April, 1941.
- Entenman, C., Chaikoff, I. L. and Montgomery, W. L.: *J. of Biol. Chem.*, 137:699, Feb., 1941.
- Feldmann, Maurice: *Radiology*, 36:224, Feb., 1941.
- Flynn, James M.: *Am. J. Roent.*, 45:380, 1941.
- Franco, S. C.: *Am. J. Dig. Dis.*, 8:65, 1941.
- Friedenwald, J. and Morrison, T. H.: *Review of Gastro-Enterology*, 8:400, 1941.
- Greengard, H., Stein, I. F. and Ivy, A. C.: *Am. J. Physiol.*, 134:244, 1941.
- Gulzow, M.: *Zeit. f. Klin. Med.*, 138:76, 1940.
- Hug, E.: *C. R. Soc. de Biol.*, 134:163, 1940.
- Hunt, V. C.: *Ann. Surg.*, 114:570, 1941.
- Ireneus, C., Jr.: *Arch. Surg.*, 42:126, Jan., 1941.
- Jeffery, F. W.: *Canad. Med. Ass'n J.*, 45:224, 1941.
- Kauer, J. T. and Glen, F.: *Arch. Surg.*, 42:141, Jan., 1941.
- Kennard, Harrison E.: *Surgery*, 9:65, 1941.
- Koucky, J. D., Beck, W. C. and Todd, M. D.: *S. G. O.*, 73:113, 1941.
- Krieg, Earl G.: *Ann. Surg.*, 113:364, March, 1941.
- Lewison, E. F.: *J. Lab. and Clin. Med.*, 26:190, 1941.
- Lewison, E. F.: *S. G. O.*, 72:202, Feb., 1941.
- Liedberg: *Acta Chir. Scand.*, 83:261, 1941.
- Loe, Ralph H.: *Northwest Medicine*, 40:127, April, 1941.
- Longenecker, H. E., Gavin, G. and McHenry, E. W.: *J. Biol. Chem.*, 139:611, 1941.
- Luke, J. D.: *Can. Med. Ass'n J.*, 45:59, 1941.
- Martin, H. B.: *Brit. Med. J.*, 1:481, 1941.
- Mekler, A.: *J. Biol. Chem.*, 141:19, 1941.
- Montgomery, W. L.: *Ibid.*, 141:1, 1941.
- Montgomery, W. L. and Nelson, C.: *J. Biol. Chem.*, 141:1, 1941.
- Moreland, Randall B., Freeman and Bromley, S.: *Surgery*, 9:712, 1941.
- Ochsner, Harold C.: *Am. J. Roent.*, 45:718, 1941.
- Ogilvie, Robertson F.: *Brit. J. Surg.*, 28:362, 1941.
- Orr, T. G.: *S. G. O.*, 73:240, 1941.
- Poppel, M. H. and Levy, A. H.: *Radiology*, 37:174, Aug., 1941.
- Popper, H. L. and Plotke, F.: *Surgery*, 9:706, 1941.
- Popper, H. L. and Sorter, H. H.: *Proc. Soc. Exp. Biol. and Med.*, 38:384, 1941.
- Rhodes, George K.: *Western J. Surg.*, 49:226, 1941.
- Schiller, W.: *S. G. O.*, 72:70, Jan., 1941.
- Scott, V. B., Collignon, U. J., Bugel, H. J. and Johnson, G. C.: *Am. J. Physiol.*, 134:208, 1941.
- Shapiro, B. and Wertheimer, E.: *Arch. Int. de Pharm.*, 64:265, 1940.
- Schnedorf, J. G. and Orr, T. G.: *Ann. Surg.*, 111:603, 1941.
- Smith, Ernest E. and Bonis, Alexander: *Am. J. Roent. and Radium Therapy*, 46:64, 1941.
- Snell, A. M. and Comfort, M. W.: *Am. J. Dig. Dis.*, 8:237, 1941.
- Sprout, E. E. and Sanders, E. K.: *Am. J. Physiol.*, 135:137, 1941.
- Taylor, A. and Agren, G.: *Acta Physiol. Scand.*, 1:79, 1940-41.
- Thomas, J. E. and Crider, J. O.: *Am. J. Physiol.*, 134:657, 1941.
- Thomason, T. H.: *Southern Surgeon*, 10:135, Feb., 1941.
- Trimble, L. R., Parsons, J. W. and Sherman, C. P.: *S. G. O.*, 73:711, 1941.
- Walters, W. and Cleveland, W. H.: *Arch. Surg.*, 42:819, May, 1941.
- Whipple, A. O. and Baumann, L.: *Am. J. Med. Sci.*, 201:629, March, 1941.
- Whipple, A. O.: *Ann. Surg.*, 114:512, 1941.

# A Plea for Early Diagnosis of Cancer of the Colon

By

KNOX BRITTAI, M.D.  
ROCHESTER, NEW YORK

**P**ATIENTS with cancer of the anus, rectum or colon, will put off having an adequate investigation longer than those with any other form of this disease. This is particularly unfortunate in view of the fact that a large majority of large bowel cancers can be diagnosed easily in the early months of their existence. To discover why people are so tardy in seeking medical consultation and a correct diagnosis, the histories of eighteen cases of large bowel cancers of mine and all such cases admitted to "The Rochester General Hospital," between 1930 and September 30, 1941, were reviewed.

During 1939, while accidents caused 120,000, respiratory diseases 92,000 and tuberculosis 62,000 deaths, the various forms of cancer killed 154,000 people in these United States. Approximately seven-tenths per cent of these deaths were due to cancer of the rectum and colon. In Rochester, N. Y., a city of about 325,000 inhabitants, there were in 1939 and 1940 respectively 96 and 119 deaths due to this form of malignancy. Such destruction of life certainly constitutes a definite menace to the human race and should challenge the interest of every member of the medical profession.

The chief cause of failure to cure cancer of the large bowel is late intervention and not a lack of operative skill. While the patient, completely ignorant of the significance of his early symptoms is partly responsible, the first consulted physician, who fails to realize the importance of the complaints, must shoulder much of the blame.

Since cancer, in its early existence, produces no specific signs and disturbs the usual bowel habit so little, the physician will always do well to suspect malignancy until its absence is proven. Though practically all cancers of the rectum can be easily diagnosed, once the patient presents himself, few diseases are diagnosed so late in their course. Gross blood in the stool is unessential to making a diagnosis of cancer of the large bowel and yet comparatively few of the patients fail to give a positive occult blood test of the stool.

Unless a sigmoidoscopic investigation is included, few gastro-intestinal examinations should be considered complete. Certainly the finding of a benign condition, such as hemorrhoids or a fissure, should never deter the physician from requesting a roentgenologic examination of the entire colon.

The 207 studied cases were divided into three groups, namely: (a) the rectal group including all cancers of the anus, rectum and recto-sigmoid, numbering 104 cases or 51 per cent of the total; (b) the left colon group including the cancers of the sigmoid, descending and splenic colon, numbering 57 cases or 26 per cent of the total, and (c) the right colon group including cancers of the cecum, ascending,

hepatic and transverse colon, numbering 46 cases or 23 per cent of the total.

The symptoms of cancer of the large bowel have been divided into three stages by Graff: (a) the stage of clinical latency; (b) the stage of gastro-intestinal manifestations, a correct interpretation of which determines the fate of the patient, and (c) the stenotic stage. In the present series, bleeding was recorded as the chief complaint or a concomitant symptom in 67 per cent of the rectal cases, which is somewhat lower than the percentage usually recorded. However, in this analysis, the patient's answer to the question concerning the presence of blood was accepted as final. In 77 per cent of the rectal group there was some change from the usual bowel habit, such as constipation, diarrhoea or a frequent urge to defecate. Abdominal or rectal distress, such as cramps, soreness, pain or discomfort was noted in 39 per cent and loss of weight in only 38 per cent of the group.

Table I shows a comparison of the frequency of the

TABLE I  
*Frequency of symptoms in each group*

|                | Rectal | Left Colon | Right Colon |
|----------------|--------|------------|-------------|
| Bowel changes  | 77%    | 60%        | 50%         |
| Pain           | 39%    | 67%        | 54%         |
| Blood          | 67%    | 33%        | 21%         |
| Loss of weight | 38%    | 44%        | 53%         |
| Weakness       | —      | —          | 24%         |

various complaints in each group. It is to be noted that blood in the stool and changes in the bowel habit decrease in frequency as the right side is approached. In 1913, Mayo emphasized the frequency of secondary anemia and the comparative rarity of obstructive signs in cancers of the right half of the colon. These right sided lesions are prone to mimic the symptoms of appendicitis, gastric ulcer or gall bladder disease.

The interim between the onset of the symptoms and the establishment of a correct diagnosis varied from a few hours in cases of obstruction or perforation to several years in those cases complaining of bleeding or changes in the bowel habit as the only primary symptoms. While the average interval was nine and one-half months, there were 163 cases in which a delay of from three months to two years occurred. Fifty-five per cent of these patients with a delayed diagnosis had not consulted a physician, but the remaining 45 per cent had been under the care of a physician without the cancer being detected. Stebbins and Burke found that of 134 palpable rectal cancers only sixty-

two per cent were correctly diagnosed on admission to the hospital.

An example of this type of procrastination is the case of a female, aged 36 years, who entered the hospital, complaining of being "weak and wobbly." She had been having abdominal pain for the past four years and noticing bloody stools during the last twelve months. Various diagnoses such as colitis, ovarian dysfunction, psycho-neurosis, hemorrhoids and spastic colon had been made. She had been given 27 injections of ovarian substance, many colonic irrigations and been treated by chiropractors. Actually, however, she had an advanced cancer of the ascending colon.

Laboratory studies failed to aid materially in establishing a correct diagnosis. The average red cell count in the rectal group was 4,400,000 and 3,900,000 in the right colon group. The average white cell count for the entire series was 8500. The chemical estimation of the blood chlorides, non-protein nitrogen,

dence to prove that cancer of the rectum may frequently be prevented by the early recognition and treatment of these lesions. Polyps were found in only six per cent of the entire series, which is somewhat lower than that found by Dukes in a study of autopsied cases.

Combining the twenty-one cases, considered inoperable on admission with the seventy-four cases which were found to have metastases at operation, one finds that 46 per cent of the lesions might be considered incurable when first diagnosed.

Inasmuch as cancer of the large bowel occurs more frequently than cancer of the stomach or cancer of the female genitalia, it is difficult to understand why all other body orifices are so diligently examined for malignancy and the large bowel so woefully neglected.

From this study two individuals appear to be responsible for the late diagnosis of large bowel cancers, namely the patient and his first consulted physician. The patient, completely ignorant of the frequency of this disease, its early manifestations, and the vital importance of early diagnosis, attributes his bleeding, tarry stools, indigestion, diarrhoea, abdominal discomfort or constipation to some dietary indiscretion or to piles. He fails to realize that these apparently insignificant signs may spell cancer, just as much as loss of weight, anemia, and cachexia and that once cancer cells have invaded such vital organs as the liver, the condition is hopeless. No less a factor in causing this procrastination is his fear of all rectal examinations, cancer itself, and the possibility of a colostomy bag.

Some physicians consider themselves too busy, some lack an interest in or have an aversion for all rectal diseases, while others place complete reliance on the ability of the Roentgen-ray to discover all cancers of the large bowel, regardless of their location. Still others are too ready to discontinue the investigation as soon as some benign condition, such as hemorrhoids, fissure, gastric ulcer, or gall bladder disease is detected, apparently never suspecting that a cancer could exist in the same patient. In spite of the fact that nearly three-quarters of all large bowel cancers are located within the lower ten inches of the bowel and therefore within easy reach of the sigmoidoscope, the barium enema is still frequently requested as the one means of discovering cancer of the large bowel.

While an active campaign, such as that used against tuberculosis might result in some cancer hysteria and phobia, neither of these conditions kills the victim, while cancer does. An educational campaign coupled with the routine use of an adequate bowel investigation should lead to the discovery of more bowel cancers in a stage when a cure could be expected.

TABLE II

*Conditions treated prior to discovery of a cancer*

| Cases       |    | Cases                |   |
|-------------|----|----------------------|---|
| Hemorrhoids | 15 | Gastric ulcers       | 3 |
| Anemia      | 8  | Coronary disease     | 1 |
| Diarrhea    | 5  | Gall bladder disease | 1 |
| Colitis     | 4  | Urinary frequency    | 1 |
| Herniae     | 2  | Salpingitis          | 1 |
| Cataracts   | 2  | Uterine suspension   | 1 |
| Goitre      | 1  | Chronic appendicitis | 1 |
| Psychosis   | 3  |                      |   |

etc., were often within normal limits even though there was definite evidence of intestinal obstruction.

Again and again the fallacy of placing absolute reliance in a negative roentgenologic report has been reiterated, but it will bear repeating at this time. Should all other signs indicate the presence of malignancy, surgical exploration should be carried out regardless of a negative X-ray report. In the present series there were ten cases, six of which had rectal cancers, reported as roentgenologically negative.

In Table II are listed the various conditions that were treated shortly before the cancer was detected. These missed opportunities for diagnosing the bowel cancers were taken from the history charts and in no wise incriminate any member of the staff of "The Rochester General Hospital." Thirty-five of these 49 cases had a cancer situated in the rectum or recto-sigmoid, areas well within reach of the sigmoidoscope.

Bowing and Dixon feel that we have sufficient evi-

## Nutritional Problems in Wartime\*

By

CLIFFORD J. BARBORKA, M.D.  
CHICAGO, ILLINOIS

WE have been engrossed so long in perfecting machines that we have forgotten the nameless and indispensable force behind them, man. We have studied the nutritional needs of our domestic animal, we have replanted our forests and dust bowls, we have built dams and irrigation ditches, but only very recently have we begun to be aware that there is such a thing, too, as human erosion.

We have taken the human being for granted. We have worked more or less on the old theory that what was good enough for grandfather was good enough for us, forgetting that the soil and the foods in grandfather's day and the conditions of that civilization differed tremendously from the modern mechanized civilization of today, and the requirements of a warfare in such a civilization. Sadly enough, not until war threatened a rich and wasteful land did the nutrition of mankind become a matter of national policy. For even in this mechanistic age wars must be waged by men, not robots, and these men must be physically fit.

No longer should a patient be dismissed with the time-worn phrase, "There is nothing physically the matter with you," and the assumption that he has an imaginary or a nervous reaction responsible. Too many times the diagnosis of chronic nervous or physical exhaustion has been substituted due to the lack of diagnostic criteria to pigeon hole the case as a diagnostic entity. If nothing can be found physically or organically to account for the distress the patient manifests, not until all the light afforded by modern means of diagnosis of nutritional deficiencies is thrown upon the case in question, should we assume that there is not some malfunction of the physiological mechanism that may be responsible for the earliest manifestations of sub-clinical states of deficiency disease.

Malnutrition is accompanied by manifold signs and symptoms, diverse in nature, and to the casual observer their origin and significance are not always apparent. Some types of malnutrition are strikingly obvious to every one, some are apparent only to the physician who looks for them and some are vague and elusive even to the careful observer using the most accurate specialized technics. If the first group alone is counted, the prevalence of malnutrition will be recorded as low, almost negligible. If the second group is counted, it will be recorded as high. If the third group is included, then the rate will be sufficiently high to occasion genuine concern.

Deficiency disease is a question that should hold the attention of the intelligently progressive clinician as a challenge. It is true that the human body can stand a lot of depletion. Vitamin deficiencies viewed experimentally may take from three to six months to manifest themselves even under laboratory, to say

nothing of clinical observations. Marginal states of nutrition, it is true, may be maintained in man for fairly long periods until the advent of some secondary pathological state or illness or some extreme stress or strain increases the demands over and above the limited intake, and, therefore, brings the deficient state to light.

We should not bury our heads in the sand and disregard the results of carefully planned studies that have clearly demonstrated the wide spread incidence of nutritional deficiencies nor should we accept the snap judgment of those whose views are colored by hit and miss observations as compatible with scientific progress.

Hunger and famine have always contributed to the defeat of armies and the subjugation of nations. Wars are won or lost according to the health, courage, and calmness of whole populations, and the ability to exert themselves to the utmost is particularly true in modern total warfare. The safety of our country is at stake. Its defense demands power, all that can be mustered, not only man power for the armed forces, but man and woman power for industry, courage and endurance in the home, health and fortitude behind as well as on the fighting lines.

The responsibility of all of us as specialists is to carry the fundamental message to groups of doctors in general practice throughout the country that they in turn are in a position to carry on the legitimate educational efforts of our National Nutritional Program.

To begin with, let me define the problem of nutritional deficiency. When we speak of the term sub-clinical state of deficiency disease, we are not speaking of an obvious deficient state such as beriberi, pellagra, scurvy, or rickets. Their symptoms are impressive, but their incidence is small. The manifestations of sub-clinical deficiency states may be long delayed depending on the degree of dietary inadequacy, the period of exposure to bad diet, or the secondary pathological states that may interfere with absorption and utilization of a good diet. Thus, functional debility may be apparent long before nutritional disease appears. This may be mild or severe.

The respiration and growth of cells involves the synthesis of complex substances from simpler chemical compounds. By means of substances called enzymes, the cells are able to perform these functions without increased temperature or pressure. Enzymes are catalysts produced by living cells from combinations of organic substances including the vitamins. These enzymes retain activity even when separated from the living cell. When a dietary deficiency of vitamins has existed over a long period of time, a biochemical lesion develops in the cell often severe enough to cause functional disturbances. If the deficiency is not corrected, these disturbances become more wide spread

\*Read before 45th Annual Meeting of the American Gastro-Enterological Association, Atlantic City, N. J., June 8-9, 1942.



and eventually give rise to an infinite variety of symptoms forming a complex clinical picture. Finally, severe or persistent alterations lead to a structural change or structural changes in the tissue, and ultimately the lesion of a deficiency disease is likely to appear.

The term sub-clinical state of deficiency disease has been employed by physicians to describe the early sub-critical states of disease that could not be recognized by available methods of examination readily. The term, naturally, is in disfavor because it is too often used as a cloak for ignorance.

#### EVIDENCE OF EXTENT OF MALNUTRITION

The present food problems of the European nations, the blockades, the submarine activities, the famines, the rationings, the use of food as a weapon of war, have, of course, been dramatized in the press to the extent that we are apt to lose sight of our own nutritional problems. Compared to the countries of Europe, of course, America is well fed, but we cannot afford to judge ourselves by external standards. We should judge ourselves by our potentialities, our resources in food, in technical developments, and in scientific knowledge. By that standard, we fall far short of our goal.

Evidence on which the prevalence of malnutrition of pre-clinical or sub-clinical states of deficiency disease is based has been recently discussed by Joliffe (1), McLester and Sherman from the food and nutrition Board of the National Research Council. They state that the evidence at our disposal warrants the conclusion that dietary inadequacies and malnutrition of varying degrees are of frequent occurrence in the United States and that the nutritional status of an appreciable part of the population can be distinctly improved. If optimal nutrition is sought, not mere adequacy, then widespread improvement is possible.

Other evidence is suggested by the following: First, the fact that in 1936 more than 40% of the families in the land had incomes too small to buy the foods they needed. Second, the fact that food purchased by from 40% to 64% of city workers provided diets which were rated poor. Third, the fact that similar surveys conducted in Canada, at Halifax, Quebec, Toronto, and Edmonton, where living is much like that in the United States, yielded statistical results similar to those in the United States. Fourth, there is the experimental demonstration with controlled laboratory study that diets comparable to the survey diets rating poor are not enough to maintain emotional and physical stability, thus, the experimental evidence on man verifies the numerous experimental suggestions in animals. Fifth, there are the studies of many population groups which reveal much debility, anemia, low values of Vitamins A, B and C in the blood, and anatomic evidence of malnutrition in the eyes, the skin, the mouth and the teeth.

#### PROBLEMS IN SECURING ADEQUATE NUTRITION

There are plenty of problems to face in putting nutrition knowledge to work in this country. Not the least of these results from low incomes. Many families just do not have enough cash income to buy the right kind of food, and they may not live where they can earn this; or even if they should earn an increased

income adequate to meet the expenditures to procure the adequate amount of food, the tremendous problem of educating, immediately in our present war emergency, these people as to the securing of the proper intake and the expenditure for this intake, is a truly major nutritional problem in war time.

Several Federal agencies have been attacking the problem in practical ways. The school lunch program, sponsored and administered by local community agencies, provided one good meal a day for about 4,000,000 children last year, and this plan and program is being expended to reach many more. The low cost milk is provided in many communities to families who cannot afford the prevailing prices. The food stamp plan is being extended to more cities so that families on relief may make their food dollar go farther toward providing the right food for their families. State and local nutrition committees recognize the need and are co-operating with the many agencies in the educational program to convey the basic knowledge to all of our population.

There are many problems of food production and distribution. The Secretary of Agriculture, Wickard, has asked the American farmers to produce more food, especially protective foods, milk, meat, eggs, vegetables and fruits, foods that have been considered the foundation of the protective factor. The primary purpose of the nutrition division of the defense health and welfare services is to see that every man, woman and child of the United States receive the information regarding nutritional relationship to obtaining full health and vigor and make the most use of it. In this nutritional educational program we must stimulate, inform, and apply the knowledge. We must stimulate every citizen to realize his own potential optimum health and well being and to strive to obtain it by every means at his command. We must inform every citizen with regard to the simplest facts concerning food values, given in simple, practical methods so that he knows how to select the right food. The application of these simple truths of nutrition in the life of every citizen of this country demands the co-operation of both industry and the consumer. The farmer must produce the right kind of food. Transportation and storage must be perfected so that food may reach the retailer in good condition.

There are pitfalls and dangers in any nutrition program. Some people will always exploit nutrition propaganda for personal gain, and there are those who will listen to quacks and charlatans. Others will take a distorted view, either overemphasizing certain phases or discounting the whole program and taking pleasure in expanding their ideas and ridiculing constructive efforts. There are those who become so enthusiastic about the potential benefits of synthetic vitamins that they have little faith in the protective foods and well planned meals. They may spend money unwisely on vitamin concentrates when the same money spent for good food might benefit themselves and their families far more. In any surge of interest in a new movement there are these dangers, but fortunately the pendulum eventually swings back to the middle of the road. Interest in nutrition is spreading, and it is the duty of those who are informed to convince the uninformed that the knowledge of nutrition is worth having and applying practically.

## PROTECTIVE FOUNDATION FOODS FOR GOOD NUTRITION

A guide to serve as a goal to good nutrition and as a yardstick by which to measure progress toward that goal has long been needed.

A simple plan for everyday living is suggested in Table I which includes the protective foods each day as a foundation to aid in meeting the recommended food allowances. This quantity and quality contains approximately 1,800 to 2,000 calories, 70 grams of protein, .93 grams of calcium, 22 mg. iron, 6,105 units of Vitamin A, 1.8 mg. of thiamin, 2.3 mg. of riboflavin and 129 mg. of ascorbic acid. With the additional foods that will be eaten to meet the various energy requirements, the recommended daily allowances of 2,100 to 4,500 calories, 60 to 70 grams of protein, .8 to 1.5 grams of calcium, 10 to 15 mgs. of thiamin, 1.8 to 3.3 mg. of riboflavin, 12 to 23 mg. of nicotinic acid, 50 to 100 mg. of ascorbic acid and 400 to 800 units of Vitamin D should be adequately available. It should be understood that these allowances are for persons in health and under ordinary circumstances.

The need may be greatly altered when conditions such as illness, increased working hours, extremes of temperature to which workers are frequently exposed, increased perspiration, speedup of work, insufficient rest, which increases energy consumption and produces a proportionate increase in the body's nutritional requirements. The need may be greatly altered in other diseases, especially those of the alimentary tract, which interfere with normal absorption, increased destruction or diminished utilization of vitamins.

TABLE I

*Protective foods each day as a foundation to aid in meeting recommended food allowances*

|  |   |
|--|---|
| Milk .....   | 1 pint for adults, 1 quart for children           |
| Egg .....  | 1   |
| Vegetables .....   | 3 large servings besides potato (one green leafy) |
| Fruit .....  | 2 servings (one raw)                              |
| Meat, fish or fowl..                                       | 1 serving (about 2 oz.)                           |
| Butter .....   | 1 tablespoonful                                   |
| You need wholegrain products and enriched bread every day. |   |
| Example:   |   |
| Cereal.....  | wholegrain or enriched (1 serving)                |
| Bread.....   | wholegrain or enriched (3 slices)                 |
| Then eat additional foods as you like.                     |   |

## MAN AND WOMAN POWER IN INDUSTRY

Experience abroad has demonstrated the fundamental importance of measures to maintain the health and morale of civilians. While these measures should apply to all classes of the population, the working efficiency of employees in defense industries is at present a matter of particular concern.

Nutrition is not the only factor in health and morale, but it is one of the most important factors. The improved health and morale which result when inadequate diets are brought up to adequate levels may be translated into greater working efficiency, fewer absences from work, and a decrease in the number of accidents.

The first and most important step in the campaign to improve the nutrition of defense workers is the provision of diets of natural foods, rich in all the essential

food factors. Supplementing the diet with synthetic vitamins may be shown to be necessary in particular instances by dietary and nutritional studies.

The discovery of vitamins, their isolation, and finally their synthesis, represents an enormous advance in the science of nutrition. It would be a tragedy should their indiscriminate use in unskillful hands throw discredit on their tremendous potentialities for human benefit.

## ADMINISTRATION OF VITAMINS TO WORKERS IN INDUSTRY

There can be no question on the part of certain commercial firms that they exploit the use of vitamins in industries. As a result the joint council (2) on Foods and Nutrition and the council on Industrial Health, recognizing the great significance of vitamins to human nutrition and the importance of vitamins when properly used, have rendered a valuable service to humanity by disapproving of the mass indiscriminate administration of vitamins to industrial workers.

In order to evaluate the proper relationship of this important nutritional problem in war time, let us ask ourselves some questions and attempt to formulate a sane conclusion.

1. Is it irrational to indiscriminately administer vitamins from the therapeutic point of view?

It is not rational to administer vitamins to the healthy worker on an adequate diet.

It might be contended that difficult muscular effort such as the industrial workers must exert with consequent greater combustion of carbohydrate should lead to a greater requirement of vitamins. Such evidence as has been secured in relation to this particular question of fatigue, however, does not support the idea that vitamin administration is of value to healthy men subsisting on an adequate diet.

Keys and Henschel (3), at the University of Minnesota, carefully tested the value of supplementing a U. S. Army ration with little amounts of available vitamins. It was concluded that supplementation of an adequate diet with additional vitamins serves no useful purpose. Foltz, Ivy and Barborka (4 and 5) likewise found no influence on fatigue or muscular efficiency by parenteral injection of vitamin concentrates in any individuals already on an adequate diet. Students of nutrition would doubtless anticipate such results.

It is admitted that a survey of the natural foods served in industrial plants and average lunch rooms revealed that there was much room for improvement, and that little attention has been paid to the kinds or quality of foods served.

The use of natural foods, to improve nutrition, regardless of whether the individual is normal, or moderately or severely deficient is still a goal, not a realization. It requires revolutionary changes in food sources and food habits, which will take years to bring about. Furthermore, the worker with the sub-clinical type of vitamin deficiency requires a higher intake of vitamins than that needed to maintain optimum health in the normal individual, and such higher intakes would be still more difficult to procure from natural foods. This would be no more rational from the therapeutic point of view than the assumption that the mass administration of vitamin capsules was the cure-all.

In contrast to this plan, it is rational from the therapeutic point of view to administer vitamins to

those individuals who do not receive an adequacy of them in the diet. The discriminate administration of vitamins to meet the approximate daily recommended requirements to all the workers is immediately available, is practical, and serves the purpose of increasing the nutritive value of the food available to the worker today. It may have, therefore, a definite place in the program aimed at improving industrial health in the absence of a better and more practical way to do it, at least, as a stop-gap in our war emergency, until the ideal program proposed by the National Nutrition Conference can be practically accomplished by the education of our nation.

2. Is it unwise nutritionally to use vitamins because special vitamin preparations cannot take the place of valuable natural foods in achieving the completely satisfactory nutritive state?

Vitamins are not intended to take the place of foods, but to supplement them. Carbohydrates, fats, minerals, proteins and many other elements are just as essential, but the vitamins are indispensable for their proper utilization; and whereas it is relatively easy to provide for the necessary bulk elements in the diet, it is often difficult under existing conditions to always provide for adequate vitamin intake from natural foods.

3. Can a good diet provide all that vitamin preparations have to offer? Even if we assume that this is true, can we be sure that the industrial worker will spend his income wisely for a good diet in place of aggravating his condition by spending it for alcohol, sugars, etc. There is evidence that the majority of individual workers do not eat a good diet. If foods were as well selected as they might be in the light of modern nutrition and knowledge, the need for any administration of vitamins should be comparatively rare—but there is evidence that the foods are not as well selected as they should be. That is why supplements of vitamins may be needed. Those who have made a sincere attempt to select foods as available today for a mixed diet to supply adequate amounts of each and every vitamin for optimum nutrition, recognize that neither the worker's family nor the plant cafeteria nor the corner lunchroom can be expected to do it. It takes almost an expert to do it, and even he will find it difficult. A good diet of adequate vitamin content is not readily secured from day to day by the entire population.

Wholesome natural foods are too seldom used as sources of the needed calories, viz, sugar, white bread and flour, pies, cakes, puddings, macaroni, spaghetti. None of these automatically supply adequate vitamins, some of them none at all. We do not underestimate the value and importance of a good diet with plenty of the protective foods, but there is no evidence that three so-called good meals a day, including protective foods, in practical quantities, will furnish adequate amounts of all the vitamins for optimum nutrition. This is, particularly, true when there is increased need for vitamins to meet added energy expenditure or secondary pathological factors that may interfere with absorption, digestion, or utilization of the vitamins.

4. Is the practice of administration of vitamins uneconomical?

Can a measure be called uneconomical which is at present a good method of making up for deficiencies known to exist frequently in the average American diet today? Shall we wait, especially, in the present emergency, until the foods, food prices, and food habits have been made what they ought to be and until

the housewife and chef have been educated in the proper choice, storage, and preparation of foods, or shall we take advantage now of what is available—proper vitamin supplements—to help make the nutrition of these workers at least more complete than it has been for better efficiency and greater production.

The program of the National Nutrition Conference in its effort to solve the nutritional problems facing the nation is of paramount value in winning the war.

The physician has a definite part in this program by giving sane counsel and guidance to all of the various lay agencies that are being used to teach the simple needs for adequate nutrition.

The use of natural foods to bring inadequate diets to the required level is the ideal solution of the problem. Until this plan shall have become workable, discriminate vitamin administration to the civilian or industrial worker on an inadequate diet is a sound policy.

### CONCLUSION

Those of us in medicine who are trained in nutritional science are well aware how much this science can contribute to solving the nutritional problems in war time. The efforts to do this work, however, and to do what we believe needs doing, is not without obstruction. Much apathy exists and some actual resistance. Some physicians and individuals in this country believe that people are getting all the food they need, while others in places of responsibility have yet to be convinced of the importance of the nutritional problems in war time.

Every experienced physician knows that the recognition, both subjective and objective, is very difficult. The unscrambling of symptoms is a challenge.

The future, we hope, will bring about methods whereby border-line states will be better recognized and identified, both by a better understanding of physical signs and symptoms suggestive of early deficiency states and by the help of new and more simplified laboratory tests to verify if an individual's bodily stock of vitamins is really low.

There are many gaps in our clinical knowledge of vitamins. Many problems still remain to be determined: The question as to what are safe limits of normal for the intake of each vitamin, or at what low level will symptoms appear. The problems of optimum amounts of vitamins. The inter-relationship between vitamins. The influence of other diseases on nutritive needs and the effect of nutritional deficiencies on associated disease.

However, we cannot risk delay in applying the present knowledge of nutrition. Metals and munition are, of course, vital in this warfare, but only through better food and proper nutrition will we be able to provide the strength, courage and morale to make and use the mechanistic instruments of war in a manner to bring about an ultimate victory.

### REFERENCES

1. Jolliffe, N., McLester, J. S. and Sherman, H. C.: Prevalence of Malnutrition. *J. A. M. A.*, Vol. 118: 944-950, March 2, 1942.
2. Council on Foods and Nutrition, and the Council on Industrial Health Report, Industrial Administration of Vitamins to Workers in Industry. *J. A. M. A.*, Vol. 118: 618-621, Feb. 21, 1942.
3. Keys, Ancil and Henchel, Austin: Vitamin Supplementation of U. S. Army Rations in Relation to Fatigue and the Ability to Do Muscular Work. *J. Nutrition*, Vol. 23, No. 3, 259-269, March, 1942.
4. Foltz, E., Ivy, A. C. and Barborika, C. J.: The Use of Double Work Periods in the Study of Fatigue and the Influence of Caffeine on Recovery. *Am. J. Physiol.*, Vol. 136, No. 1, pp. 75-85, March, 1942.
5. Foltz, E., Ivy, A. C. and Barborika, C. J.: Influence of Components of the Vitamin B Complex on Recovery from Fatigue. *J. Lab. and Clin. Med.*, In press.

## The Nonfunctioning Gastro-Enteric Stoma Diagnostic Study of Sixty-Two Surgically Demonstrated Cases\*

By

GEORGE B. EUSTERMAN, M.D.,† B. R. KIRKLIN, M.D.‡

and

CARL G. MORLOCK, M.D.§

ROCHESTER, MINNESOTA

**O**BSERVATIONS on the late sequelae of gastric surgical operations should always command the interest of gastro-enterologists if for no other reasons than the diagnostic difficulties frequently encountered in such sequelae. A number of contributions in which this interesting phase of gastro-enterology was considered has been made by us in the past (1-4). Although surgeons have recorded numerous observations on obstruction of the gastro-enteric stoma as an early post-operative complication, articles in which non-function of the stoma as a late post-operative complication is considered are relatively infrequent.

### CAUSATION

There are ten recognized causes of early post-operative complications of this nature. Four are directly the results of technical shortcomings, two are caused by the forming of adhesions about the stoma or distal to it, and the remaining four consist of (1) a rigid and short mesocolon, (2) pressure of the middle colic artery, (3) hypoproteinemia, and (4) anastomotic ulcer. Delayed or late post-operative obstruction of the stoma usually is attributed to the last-mentioned factor or its complications.

### DIAGNOSIS

*Differential.* Successful differential diagnosis presupposes a thorough knowledge, whenever possible, of the symptoms and conditions existing before, during and after the operation, especially with reference to whether or not an ulcer actually existed and whether gastrojejunostomy or some other type of operation was done. In the absence of reliable information in relation to these points, the gastro-enterologist, as well as the roentgenologist and gastroscopist, is thrown largely on his own diagnostic resources.

In the type of late post-operative disturbance under consideration, arrival at the diagnosis was not particularly difficult in the presence of unequivocal evidence of impaired gastric emptying, coupled with the knowledge that gastrojejunostomy previously had been performed. By the very nature of things the clinician could take it for granted that the stoma was not functioning properly. On the other hand, if information concerning essential details is lacking, the logical diagnosis in the majority of cases unwittingly would be "pyloric obstruction arising from duodenal ulcer." But, granted that the gastro-enterologist has possession of all the facts in the case, the results of roentgenologic examination are particularly illumi-

nating, even though the actual cause of the obstruction is not manifest.

*Roentgenologic aspects of diagnosis.* It is desirable for the roentgenologist to be appraised of the fact that gastro-enterostomy has been performed, for during an ordinarily brief period of examination barium may not pass through a fully patent stoma and may thus fail to disclose the anastomosis. It is also advantageous for the examiner to know who performed the operation, for he can better evaluate his observations if he is familiar with the particular surgeon's methods. The roentgenologic technic should follow the usual routine, and only a few swallows of the barium suspension should be given to the patient at first, so that mucosal relief and the stoma will be exhibited satisfactorily. Thereafter, larger amounts of the mixture can be given as needed. Chief among roentgenologic signs of a nonfunctioning or poorly functioning stoma is, of course, failure of the barium mixture to pass through the opening, or passage of it in an obviously inadequate volume. In corroboration of this sign, the cause of it may be demonstrable as gastro-jejunitis or an ulcer situated at or near the anastomosis; again the situation of the stoma too high or too low in the stomach may be rather confirmatory. But complete failure or inadequacy of the stoma to perform its function always should be established thoroughly; otherwise, errors are bound to result. Often, during the first minutes of examination, barium cannot be seen passing through the stoma, although the stoma is functionally competent. To clarify such uncertainty, the patient should be permitted to relax before the examination is continued, and the examiner should repeat his inspections until he is satisfied, or he should request re-examination later. Indeed, it is seldom safe to base a definite diagnosis of nonfunctioning stoma on the results of any single examination, but a high degree of reliance can be placed on the opinion if the test in question is repeated and reasonable care is exercised. On the other hand, ready passage of barium in adequate quantity through the stoma is conclusive evidence that the anastomosis is functioning properly. The fact that the barium is passing through the stoma must be ascertained by the examiner, for when the pylorus is not obstructed the barium in the stomach merges with that in the loop of bowel at the site of the stoma, whether the latter is functioning or not. By pressure on the proximal loop of bowel, deception can be excluded. This brief roentgenologic consideration should end on a note of caution: namely, that whenever the roentgenologic data are incompatible with the clinical

\*Read before the Forty-Fifth Annual Meeting of the American Gastro-Enterological Association, Atlantic City, New Jersey, June 8-9, 1942.

†Division of Medicine.

‡Section on Roentgenology.

§Division of Medicine, Mayo Clinic.

facts, the examinations should be repeated or results of them reexamined until they harmonize.

### MATERIAL

The patients in this series of sixty-two surgically demonstrated cases came under our observation during the period from 1924 to 1941. They were selected on the basis of a roentgenologic diagnosis of nonfunction of a gastro-enteric stoma. More than three-fourths of the patients had been operated upon elsewhere, originally. Fifty-four of the patients (87 per cent) were males, and eight (13 per cent) were females. Eighty per cent of the patients were between the ages of thirty and sixty years. So far as we could determine, the original lesion was a duodenal ulcer in fifty-six cases of the total of sixty-two; a posterior type of gastrojejunostomy had been performed in fifty-five, and an anterior type of gastrojejunostomy in one case. In four there was no demonstrable evidence of an ulcer, either from the standpoint of the history or the results of roentgenologic examination or of surgical exploration, and in two the original ulcer was gastric in situation.

### THE FACTOR OF SEX

Assuming that ulcerative or inflammatory anastomotic lesions are the most common causes of late post-operative malfunction or obstruction of the gastro-enteric stoma, the aforementioned data, that is, the preponderance of males, and of duodenal ulcer as the original lesion, and the infrequency of gastric ulcer, follow a familiar pattern. In a recent study of 155 cases of gastrojejunal ulcer, Walters and Clagett (5) showed that the ratio of men to women in the series was about fifty to one. Because of that ratio, it was felt that a circumspect survey of the pathologic process in the eight women included in our series was warranted. In seven of these eight women the obstruction was fundamentally noninflammatory and mechanical, caused chiefly by "twisting of the gastro-enterostomy on itself"; that is, a form of volvulus. Only two of the women had evidence of ulceration in the stoma, and this ulceration was associated with the volvulus just mentioned. In three of the eight women there was no evidence whatsoever of a primary gastric or duodenal ulcer. Gastrojejunitis was found to be the complicating factor in one of the only two gastric ulcers in the series.

### SYMPTOMATOLOGIC ASPECTS

*First group.* The symptoms and signs in a little more than three-fourths of the patients (77 per cent) were typical of those which characterize ulcerative or inflammatory anastomotic lesions, in addition to those engendered by reactivation of the original ulcer. There was also the added clinical feature of gastric motor impairment in 80 per cent of the sixty-two cases. In those patients in whom the obstruction was marked, toxemia, malnutrition and even tetany were often manifest. About a third of the patients had pains of greater intensity than those that had been experienced originally. Moreover, the pains were less amenable to relief by the usual measures and frequently shifted downward to the left abdominal quadrant. Extension of pain to the back and hypogastric area was not uncommon. In such cases the titer of the gastric contents was usually high. This combination of symptoms and signs is characteristic

of subacute perforating jejunal ulcer, and diagnosis of such a lesion usually was verified at operation.

*Second group.* Next in frequency and importance was a somewhat similar group of signs and symptoms in which pain was less marked and was more inclined to be localized than was the pain in the first group. The symptoms had a tendency to reduplicate the original ones. However, frequent shift of the pain to a lower anatomic level and hemorrhage were features of the second group, in common with those of the first. In the second group the surgical observations were uncomplicated marginal ulcer or gastrojejunitis.

*Third group.* A third group of signs and symptoms was characterized by obstruction of a mechanical nature and the patients had a rather nondescript type of pre-operative history and early post-operative symptoms of a stormy, obstructive nature. Achlorhydria was present in seven of the eight cases in which intubation was carried out. Such a combination of low values for gastric secretion and obstruction seems characteristic of patients who have mechanical blockage of a gastric-enteric stoma.

*Other signs or symptoms.* The late occurrence of hemorrhage after gastrojejunostomy performed for duodenal ulcer when there is no history of pre-operative hemorrhage usually is significant of an ulcerative or inflammatory process at a site other than that of the primary lesion. Such hemorrhage was recorded concerning seventeen patients in this series. It was found to have originated in an anastomotic lesion in fifteen instances and in diffuse hemorrhagic gastritis and gastric ulcer, respectively, in each of the remaining two instances. Another clinical feature which served to raise a strong suspicion of the ulcerative or inflammatory nature of the anastomotic lesion as the cause of nonfunction of the stoma was the early recurrence of symptoms after gastrojejunostomy. Including those who experienced no relief or only partial relief by gastrojejunostomy, more than 60 per cent of the entire group of patients experienced recurrence within a year post-operatively. If more careful histories in this particular respect had been taken, the percentage of recurrence, in our opinion, undoubtedly would have been higher. In a previous study of eighty-three cases of gastrojejunal ulcer verified at surgical operation one of us (Eusterman) (1) noted that 80 per cent of the patients had recurrent symptoms within a year after operation. Observations made in experimental studies lend credence to our clinical experience in this respect. Flint (6) showed that when faultless surgical technic is used, healing after gastroenterostomy takes place by "first intention" in parts of the anastomosis. But as a rule, the newly formed anastomosis is the site of a healing ulcerative surface which endures for a period of about fourteen days, and for the first five or seven days post-operatively the process is largely destructive, at least so far as the mucosa is concerned.

### PATHOLOGIC OBSERVATIONS

*Ulcerative or inflammatory lesions.* At operation a marginal or jejunal ulcer, with or without associated gastrojejunitis, was found in twenty-nine instances. In nineteen cases actual ulcer was not demonstrable surgically, but definite, obliterating gastrojejunitis, confirmed by histologic examination, was observed. Thus, in a total of forty-eight cases, or 77 per cent,



an ulcerative or inflammatory lesion, or both was found.

*Mechanical lesions.* In a second group consisting of eight patients the obstruction was either solely or predominantly mechanical, due to "twisting of the gastro-enterostomy on itself" in three cases, to improperly placed and an originally too-small stoma in four cases, and to performance of long-loop anterior gastro-enterostomy and the subsequent extensive formation of adhesions, in one case.

*Physiologic dysfunction.* In a third group comprising six cases the condition was classified as "physiologic dysfunction." In this group the surgeon had found the stoma to be open, without evidence of ulceration or inflammation. In three cases, however, the presence of an associated penetrating or perforating gastric ulcer was noted. In one of these the stoma was small and was situated too close to the pylorus, so that even if it had been functioning it would have been difficult for the roentgenologist to be sure of it under the circumstances. In a fourth case a woman had a large atonic stomach, with no reliable evidence of a previous ulcer, so far as we could determine. In all probability the same atonic condition had existed prior to the performance of gastrojejunostomy. In the remaining two cases of this group of six there was no tangible explanation for the nonfunction. In only two of the six cases was there clinical evidence of marked motor insufficiency of the stomach.

#### OBSERVATIONS CONCERNING FACTORS AFFECTING GASTRIC MOTOR FUNCTION

Certain clinical features and pathologic observations not consistent with the roentgenologic diagnosis of a nonfunctioning stoma require explanation. Under the circumstances it would not be unreasonable to presume that the stomach was blocked completely, an obviously serious state of affairs. As previously stated, routine examination disclosed evidence of undue gastric retention among four-fifths of the patients, but such retention was of marked degree among only a third of these. In such cases operation disclosed one of the following conditions: a subacute, perforated jejunal ulcer with a marked inflammatory reaction, cicatrizing obliterative gastrojejunitis, or mechanical obstruction caused by twisted loops of bowel, herniation of loops through a rent in the transverse mesocolon, or a poorly placed, originally too-small stoma that was undergoing progressive contraction. Undoubtedly, more exacting studies carried out with motor meals would have disclosed the fact that among the majority of patients retention was of a higher degree than herein recorded, because a large percentage of patients necessarily were following a restricted semisolid or liquid diet at the time of their admission. It must be concluded that a nonfunctioning stoma, from a roentgenologic standpoint, does not necessarily imply total gastric obstruction, and is compatible with a fair degree of gastric motility in the presence of pathologic changes in the anastomotic region. Therefore, two possibilities arise: either (1) such nonfunction is of an intermittent nature, the result of spasm and edema, or (2) egress of liquid and semisolid food is still possible if the nonfunction is of a persistent nature. On the other hand, roentgenologic evidence of incomplete obstruction may be consistent with serious and refractory impairment of gastric emptying. This is a much more common condition

than that under consideration, and is illustrated in the following case.

*Impairment of gastric emptying.* A white man thirty-nine years old entered the Mayo Clinic in September, 1932. Posterior gastrojejunostomy had been performed elsewhere in 1927, because of pyloric obstruction caused by a chronic, nonhemorrhagic duodenal ulcer. Partial relief had been experienced for four months. Then recurrent symptoms of progressive severity, with a shift of pain from the right part of the epigastrium to the left abdominal quadrant had supervened. In addition, for the first time, hematemesis and melena had occurred in February, 1931, and July, 1932. For three months prior to this patient's admission there had been marked nocturnal pain which had awakened him, as well as vomiting of unduly retained gastric contents. Gastric analysis disclosed gastric contents of 1250 cc., free hydrochloric acid of 28 clinical units, food remnants (graded 4) and blood (graded 1). Roentgenoscopic examination revealed a highly placed malfunctioning stoma with partial obstruction. The duodenal cap was not seen. At operation (gastric resection) on October 8, 1932, the surgeon noted the presence of a subacute perforated jejunal ulcer with impending gastrojejunocolic fistula.

Next, what is the explanation for a stoma that is closed at the time of the roentgenologic examination but which apparently is open and uninvolved at the time of the operation? In the absence of tangible evidence of gastric obstruction in such cases, it seems logical to conclude again that such nonfunction is not permanent. Also, the relaxing effect of a general anesthetic agent, in the event the closure is of a spastic nature, must be considered. In this respect it is appropriate to call attention to the fact that during an emergency operation for refractory gastric obstruction supervening soon after the performance of gastrojejunostomy surgeons sometimes are surprised to discover that the stoma is open. Such a phenomenon has been attributed to disturbance in the function of the gastric musculature, such as occurs in hypoproteinemia or adynamic ileus. It is not improbable that some incompletely understood type of dysfunction of the gastric musculature plays a similar role in the late sequelae of gastrojejunostomy.

Gastroscopic examination seems particularly indicated in those cases in which the clinical observations are not consistent with the roentgenoscopic ones, especially in those cases in which gastric motility does not seem to be impaired. Such examination also may disclose the fact that the stoma can be open, even though it is found to be nonfunctioning during the roentgenoscopic examination. In that event the latter examination should be repeated, and the functioning of the stoma should be watched for a longer period.

*Patent stoma demonstrated by gastroscopy.* A white woman thirty-three years old had symptoms of peptic ulcer since the age of nine years. A diagnosis of chronic duodenal ulcer, confirmed by roentgenologic examination had been made at the Mayo Clinic in August, 1927, when the patient was twenty years old. She underwent gastrojejunostomy, performed elsewhere, a month later. She entered the clinic a second time in May, 1941. She had experienced severe hematemesis and melena in 1937 and 1940, as well as occasional episodes of heartburn and nocturnal gaseous distention, but she never had had any pain. Gastric analysis (Ewald) revealed: total acidity, 38 clinical units; free hydrochloric acid, 28 clinical units; amount of contents 270 cc. Roentgenologic examination disclosed the bulbar deformity of an old duodenal ulcer without a crater or pyloric obstruction. One of us (Kirk-



lin) reported that evidence of a gastro-enteric stoma was absent. Gastroscopic examination disclosed very extensive chronic erosive and perianastomotic gastritis and a wide-open, properly placed stoma. Operation was not performed. This patient presented the clinical evidence of prolonged gastric emptying time. Improper functioning of the stoma, demonstrated roentgenologically, undoubtedly played a role in her condition, in spite of an apparently patulous stoma.

That a patient may have persistent roentgenologic evidence of nonfunction for a period of years, with variable degrees of gastric retention and still maintain a fair state of health without resorting to surgical intervention, is illustrated by the following report.

*Persistent nonfunction of stoma and variable gastric retention, but fair health.* A white woman seventy-three years old had undergone posterior gastrojejunostomy for chronic obstructing duodenal ulcer at the Mayo Clinic in 1915 at the age of fifty-one years. She had experienced good health thereafter for sixteen months. Then rather nondescript dyspepsia recurred. The patient was admitted a second time in March, 1918. Gastric analysis disclosed: content, 300 cc.; free hydrochloric acid, 28 clinical units; food remnants, grade 2; sarcinae and yeasts. Roentgenologic examination revealed a bulbar deformity of duodenal ulcer, but the gastro-enteric stoma was not seen by the late Dr. Carman. Fair health followed intensive treatment for ulcer. Then, in 1925, after a period of hard work and fatigue, she experienced high-grade gastric retention and rapid loss of weight. Roentgenologic examination at that time (carried out elsewhere) disclosed obstruction at both the pylorus and the site of anastomosis. The patient again was hospitalized for five weeks, for treatment. Thereafter she was much improved and remained so for more than a year, gaining 30 pounds (13.6 kg.). Because of recurrence, similar, temporarily successful, treatment was carried out in 1927, and in February, 1929. The patient entered the clinic for the third time in May, 1929, because of anemia, diarrhea, a retention type of vomiting, vitamin deficiency, a toxic state and gastric tetany. Roentgenoscopic examination on May 7, 1929, again disclosed a duodenal deformity and absence of a gastro-enteric stoma. Similar roentgenologic observations were made four days later. On May 27, 1929, there was only very slight gastric retention six hours after the patient had ingested a barium motor meal, but again a gastro-enteric stoma was not seen. Identical roentgenologic observations were made in August, 1929. The patient again consulted us on July 28, 1930, saying that during the previous year she had enjoyed fairly good health because she had closely followed a prescribed regimen for ulcer. At that time gastric analysis disclosed: contents, 50 cc.; free hydrochloric acid, 26 clinical units. Roentgenologic examination disclosed the familiar deformity of the duodenal cap, but not the gastro-enteric stoma. The patient was last seen in October, 1938; she consulted us chiefly because of a recent attack of cystitis. At that time she experienced only an occasional mild bout of dyspepsia. Gastric analysis on this final visit disclosed: contents 350 cc.; free hydrochloric acid, 14 clinical units; food remnants, grade 1. Roentgenologic examination disclosed a deformity of the duodenal cap, but, as on all former occasions, the gastro-enteric stoma was not seen.

Such a case illustrates the fact that as the result of ulcerative or inflammatory lesions in particular, obstruction of the stoma is not absolute, and in instances in which the stoma is open there may be no actual clinical obstruction, even though the stoma is not functioning at the time of the roentgenoscopic examination. Complete obstruction, associated with a stormy and dangerous course may, however, obtain when one or both loops of bowel is obstructed, as was true in a

case reported by one of us (7). In such instances obstruction invariably is of a mechanical nature, chiefly the result of volvulus, extensive adhesions which involve one loop or both loops (usually the distal one), or herniation of the loops through the rent in the transverse mesocolon.

In our opinion the added presence of pyloric obstruction increases the motor insufficiency of the stomach. It is reasonable to presume that this is the result of increased dilatation of the organ; that is, myasthenia gastrica. Such a type of obstruction may exist at the time of the original operation and persist post-operatively if the ulcer was of the encircling type and was undergoing cicatrization. But such obstruction also may occur after operation in cases in which it had not existed before, as a result of reactivation of the original ulcer or formation of a new one when difficulties at the new outlet arise. The post-operative symptoms and signs may faithfully portray such recurrence at the original site, and this is usually confirmed by the surgical observations. Moreover, the ulcer frequently is of the perforating type, with an associated inflammatory mass, a type of complication which undoubtedly contributes directly to the obstructive phenomena.

#### SUMMARY

Roentgenoscopic demonstration of a nonfunctioning gastro-enteric stoma is an infrequent late post-operative phenomenon.

The preponderance of the condition among males, of duodenal ulcer as the original lesion, of primary post-operative gastro-enteric hemorrhage, and frequent shift of pain and tenderness to the left abdominal quadrant are clinical features which strongly imply that the causative factor is an ulcerative or inflammatory process involving the anastomosis. Such symptoms and signs typified the clinical picture presented by three-fourths of the sixty-two patients comprising this series.

Surgical observations were: (1) marginal or jejunal ulcer and gastrojejunitis in forty-eight patients, or 77 per cent; (2) mechanical conditions, such as volvulus and extensive adhesions (chiefly involving the loops) in eight patients, or 13 per cent; and (3) no surgically demonstrable abnormality of the stoma in six patients, or 10 per cent, the condition being classified as "dysfunction."

The clinical characteristics of these three types of complications and the diagnostic significance of them are discussed.

In 90 per cent of the patients who had roentgenologic evidence of nonfunction the presence of a demonstrable pathologic process was surgically confirmed.

Although a nonfunctioning gastro-enteric stoma is associated with the implication of complete gastric obstruction, such obstruction actually is infrequent. Forty-eight out of sixty patients (80 per cent) in this series had gastric retention, but it was of considerable degree among only a third of them. There was no demonstrable impairment of gastric motor function among 20 per cent of the patients. Nonfunction may have occurred when the stoma is found to be patulous on gastroscopic examination or at operation. Explanations for disparity between roentgenologic data and clinical facts, in respect to motor function are advanced.

# REFERENCES

1. Easterman, G. B.: A Clinical Study of 83 Gastrojejunal Ulcers: Diagnosis Verified at Operation. *Minnesota Med.*, 3:517-521, Nov., 1929.
2. Easterman, G. B.: Diagnostic and Therapeutic Aspects of Late Sequelae of Gastric Surgery: Observations Based on Six Thousand, Four Hundred Operations for Chronic Gastric and Duodenal Ulcers. *J. A. M. A.*, 77:1245-1249, Oct. 15, 1921.
3. Kirklin, B. R.: Roentgenologic Determination of Normal and Abnormal Results Following Operation on the Stomach and Duodenum. *Am. J. Roent.*, 33:468-480, April, 1935.
4. Easterman, G. B. and Balfour, D. C.: The Stomach and Duodenum. Philadelphia, W. B. Saunders Company, Chap. 62, p. 866, 1935.
5. Walters, Walkman and Clagett, O. T.: Gastrojejunal Ulcer: Study of 155 Cases. *Am. J. Surg.*, 46:83-93, Oct., 1939.
6. Flint, J. M.: The Healing of Gastro-Intestinal Anastomoses. *Ann. Surg.*, 65:202-221, Feb., 1917.
7. Easterman, G. B.: A Case of Delayed Post-Operative Obstruction of the Proximal Loop of the Jejunum from Adhesions and a Description of the Attendant Phenomena Including Gastric Tetany. Discussion of the Discrepancy Between Clinical and Roentgen-ray Observations on Motor Function: Summary. *M. Clin. North America*, 5:395-399, Sept., 1921.

## Follow-Up Results in Sub-Total Gastric Resection for Ulcer\*

By

REYNOLD E. CHURCH, M.D.

and

J. WILLIAM HINTON, M.D.

NEW YORK, NEW YORK

**D**URING the past fourteen years 1256 patients with peptic ulcer were treated in the gastro-enterological clinic of the Fourth Medical and Surgical Divisions of Bellevue Hospital. These patients made 24,324 visits to the clinic or an average of over nineteen visits per patient. This vast amount of material has given us a clinical background from which we have been able to make various studies and deductions.

In one of our studies (1) published in 1934 we confirmed a suspicion that the results of long follow-up study in gastro-enterostomy cases were not satisfactory in our clinic. A later analysis of this type of operation (2) published in 1940 with an average of 7.1 years follow-up, revealed that as the years of observation increased the number of cases which were benefited had diminished markedly.

Early in 1933 when the results of our first study re-

roentgenological studies. It is our policy to make roentgenological studies every four months for the first two years and then at six month periods unless symptoms call for studies at more frequent intervals. We have also made frequent determinations of the blood picture as well as gastric analyses.

We have made every effort to evaluate the end results of the sub-total resections as critically as the end results in gastro-enterostomies. We still feel that in a disease like peptic ulcer where symptoms present a cyclic phenomenon, single observations made yearly or even after a lapse of several years can be most mis-

TABLE I  
Sex

|         | Number | Per Cent |
|---------|--------|----------|
| Males   | 95     | 92.5     |
| Females | 9      | 8.5      |

vealed the numerous failures and complications following gastro-enterostomy, we altered our operative procedure and since that time we have performed sub-total gastric resections exclusively in all cases of chronic gastric and duodenal ulcers.

In our clinic we have followed 104 cases of sub-total gastric resection which have been under our observation for an average of 2.88 years. These patients have made a total of 1822 return visits, or an average of over 18 visits each. The result is not reported in any case where the post-operative period is less than one year or the follow-up history is in any way inadequate.

The possible merit in this analysis is due (1) to the continuous personal contact between patient and physician which resulted in the studying and recording of all complaints, and (2) to frequent laboratory and

TABLE II  
Average age at onset of symptoms

|  | Number | Per Cent  |
|--|--------|-----------|
| 10-19 yrs.                                 | 4      | 4         |
| 20-29 yrs.                                 | 37     | 37        |
| 30-39 yrs.                                 | 33     | 33        |
| 40-49 yrs.                                 | 15     | 15        |
| 50-59 yrs.                                 | 10     | 10        |
| 60-69 yrs.                                 | 1      | 1         |
| Youngest patient                           |        | 16 yrs.   |
| Oldest patient                             |        | 69 yrs.   |
| Average age                                |        | 37.7 yrs. |
| Longest duration                           |        | 40 yrs.   |
| Average pre-operative duration of symptoms |        | 8.2 yrs.  |
| Average age at operation                   |        | 42.9 yrs. |

leading. There is no doubt that patients seen in an asymptomatic period seem to forget their former discomforts.

It is our policy never to accept or to use letters from patients in our follow-up studies. This method requires interpretation of the existing condition by the patient and results in an exaggeration toward a successful or unsuccessful result, determined only by the present mental attitude of the patient toward his surroundings and his physician.

Comparison of the results obtained from sub-total gastric resection for ulcer with those found after a

\*Read before the Annual Meeting of the American Gastro-Enterological Association, June 8, 1942, Atlantic City, New Jersey.

TABLE III  
*Birthplace*

|               | Number | Per Cent |
|---------------|--------|----------|
| United States | 38     | 40.0     |
| Ireland       | 12     | 12.6     |
| Russia        | 11     | 11.6     |
| Hungary       | 8      | 8.4      |
| Italy         | 8      | 8.4      |
| West Indies   | 5      | 5.2      |
| Germany       | 4      | 4.2      |
| Canada        | 3      | 3.1      |
| Britain       | 1      | 1.0      |
| Scotland      | 1      | 1.0      |
| France        | 1      | 1.0      |
| Spain         | 1      | 1.0      |
| Armenia       | 1      | 1.0      |
| India         | 1      | 1.0      |

similar period of post-operative follow-up for gastro-enterostomy should be most enlightening in determining the best operative procedure, since indications for surgery were the same in the two groups as well as the environmental and economic status of the patient.

Attempts have been made to study nationalities and occupations in this series. This report includes 95 males to 9 females, a ratio of 9 to 1. This agrees with our former findings and the already established conception of preponderance in the male (Table I).

It is apparent from this report that the majority of individuals suffering from peptic ulcer have the onset of the disease between the ages of 20 and 50 (Table II). This is the period of greatest mental and physical activity. The average age of onset of symptoms was 34.7 years, the youngest being 16 and the oldest 69. It was also found that the average duration of pre-operative symptoms was over eight years. This we believe emphasizes the growing conservatism in ulcer surgery as represented in our clinic.

The nationalities or more accurately, the birthplaces

TABLE IV  
*Occupations*

|   | Number | Per Cent |
|---|--------|----------|
| Laborer, longshoreman, rock driller   | 17     | 18.4     |
| Porter, elevator operator, building sup't, door-man, messenger, shipping clerk, hairdresser | 15     | 16.3     |
| Clerk, bookkeeper, executive, hospital attendant  | 14     | 15.2     |
| Chauffeur, truckman, bus operator, motorman   | 11     | 11.9     |
| Carpenter, painter, electrician, iron worker, machinist, factory worker                     | 8      | 8.7      |
| Housewife, maid   | 7      | 7.6      |
| Tailor, presser, cleaner, laundry worker, leather worker                                    | 7      | 7.6      |
| Salesman, collector, delivery boy   | 5      | 5.4      |
| Cook, waiter  | 4      | 4.2      |
| Fireman, policeman  | 3      | 3.2      |
| Sailor  | 1      | 1.0      |

TABLE V  
*Place of operation*

|                                  | Number | Per Cent |
|----------------------------------|--------|----------|
| Bellevue Hospital, New York City | 93     | 89.4     |
| Other New York Hospitals         | 10     | 9.7      |
| Hospitals outside N. Y. City     | 1      | 1.0      |

of patients, are shown in Table III. It is not our intention to interpret these findings as having any bearing on the incidence of the disease in those countries. There were 12 negro patients in our series.

Other observers have reported that certain confining occupations tend to produce or aggravate peptic ulcer. Also, it is believed that strenuous mental activity or worry is often associated with the onset of symptoms and in these findings we concur. In Table IV we have grouped the occupations attempting to associate as nearly as possible similar conditions, such as exposure to weather and chemicals, periods of confinement and necessary continuity of duty. In this report exposure

TABLE VI  
*Type of ulcer*

|                       | Number | Per Cent |
|-----------------------|--------|----------|
| Gastric               | 15     | 14.4     |
| Duodenal              | 89     | 85.6     |
| Duodenal and marginal | 11     | 12.3     |

to the element seems unquestionably to be a contributing factor.

To properly evaluate the end results of any report it is necessary to know the economic status of the cases. In this group all but one case was operated upon in New York City and of these 89.4 per cent were operated on in the wards of Bellevue Hospital (Table V), which is a large municipal hospital.

Duodenal ulcer was found to predominate over gastric ulcer (Table VI). In this particular study there was found to be 85.6 per cent duodenal ulcer. This is slightly under the general average of the entire 1256 cases in our clinic where 89 per cent are

TABLE VII  
*Reason for operation*

|   | Number | Per Cent |
|---|--------|----------|
| Pain alone                                  | 48     | 46.1     |
| Pain and hemorrhage                         | 37     | 36.5     |
| Pain, hemorrhage, obstruction               | 3      | 2.8      |
| Pain, hemorrhage and malign. deg.           | 1      | 1.0      |
| Pain and obstruction                        | 7      | 6.6      |
| Pain, obstruction and possible malign. deg. | 3      | 2.8      |
| Hemorrhage alone                            | 2      | 1.0      |
| Massive active hemorrhage                   | 1      | 1.0      |
| Obstruction alone                           | 1      | 1.0      |
| Malign. deg.                                | 1      | 1.0      |

found to be duodenal and also is under the 92 per cent found to be present in our studies on gastro-enterostomies. However, the greater possibility of malignant degeneration of gastric ulcers increases the number of resections for this type and accounts for the greater number of gastric ulcer cases.

Early in the organization of our clinic it was decided that all cases of peptic ulcer must be subjected to an adequate medical regimen before surgery is contemplated. The factors that may necessitate surgical intervention are given in Table VII.

1. *Severe Pain*: Under this heading comes pain which is not relieved by medication, rest or diet, and

TABLE VIII  
*Factors precipitating operation*

|                 | Number | Per Cent |
|-----------------|--------|----------|
| Pain as symptom | 90     | 95.1     |
| Hemorrhage      | 44     | 42.3     |
| Obstruction     | 14     | 13.4     |
| Mal. deg.       | 5      | 4.8      |

which is without intervals of relief or periods of remission.

2. *Hemorrhage*: This is an indication for operation if, in spite of adequate medical treatment, the patient continues to have repeated hemorrhages. These are nearly always associated with severe pain.

3. *Obstruction*: This is an adequate cause for operation if repeated roentgen examination shows a retention after six hours, associated with severe pain. However, since obstruction is caused by both spasm and edema, a conscientious effort must be made by dietary regimen and anti-spasmodics to relieve the obstruction before advising operative interference. Whenever pain is constantly present and associated with obstruction, operation is indicated.

TABLE IX  
*Type of resection*

|                                    | Number | Per Cent |
|------------------------------------|--------|----------|
| Moynihan (11)                      | 59     | 90       |
| Polya (posterior)                  | 9      | 9        |
| Finsterer                          | 1      | 1        |
| Of above dissec. of marginal ulcer | 10     | 10       |

4. *Malignant Degeneration*: If there is doubt from the roentgen studies, gastroscopy and other laboratory data, as to a differential diagnosis between ulcer and carcinoma, then operation should be immediately advised. This does not occur in over ten per cent of the gastric lesions.

Since we are interested in the relationship between the factors necessitating operation and the unsatisfactory findings following sub-total gastric resections, we have grouped in Table VIII the number of cases and the percentage of incidences of the symptoms found in this group. Uncontrolled pain was the most frequent symptom, being present in over 95 per cent of cases operated on. Hemorrhage, present in over 42

per cent, was the second most important factor and was associated with pain.

The Moynihan II type of resection was performed in this series and 65 per cent of the stomach removed. In Table IX we have grouped with percentages the types of operative procedure employed in this report. The Moynihan II resection, with anterior anastomosis, comprises the predominant number. There were ten cases where dissociation of a previous gastro-enterostomy with marginal ulcer was necessary before resection of the stomach was done.

The 97 cases in which the results have been interpreted are tabulated in three categories (Table X).

TABLE X  
*End results of sub-total resection*

|                      | Number | Per Cent |
|----------------------|--------|----------|
| Cured                | 64     | 65.9     |
| Benefited            | 24     | 24.7     |
| Total improved       | 88     | 90.67    |
| Unimproved           | 9      | 9.2      |
| Inadequate follow up | 7      |          |

1. *Cured*: Under this heading we included all patients who have been symptom-free since operation, and who have performed their customary duties besides resuming their normal position in society. There were over 65 per cent of the series in this group.

2. *Benefited*: This group included those individuals who, although suffering from a mild recurrence of symptoms or some such unsatisfactory elements, as weakness, loss of weight, or anemia, were still able to resume their former activities and gainful occupations. Although considerably benefited by operation, these cases must still observe dietary restric-

TABLE XI  
*Unsatisfactory elements in benefited cases*

|  | Number | Per Cent |
|--|--------|----------|
| Recurrence of slight pain  | 15     | 62.5     |
| Marked weight loss associated with weakness                        | 4      | 16.6     |
| Recurrence of symptoms when drinking or after dietary indiscretion | 2      | 8.3      |
| Recurrence of symptoms when emotionally upset                      | 1      | 4.16     |
| Severe anaemia (works normally)                                    | 1      | 4.16     |
| Hemorrhage recurred 22 months after operation—now normal           | 1      | 4.16     |

tions and occasionally supplement this with medication. In this group over 24 per cent of the cases were placed. It was noted that symptoms recurred on the average of 1.2 years following operation in the benefited cases. The close approximation of all cases to this figure was striking. Table XI shows the numbers and percentages of the unsatisfactory factors found in the benefited cases. Of 24 benefited cases, 4 or 16.6 per cent were not operated on at Bellevue Hospital.

Table XII shows an analysis of all the benefited cases. In this tabulation is given the number of cases,

TABLE XII  
*Analysis benefited cases*

| Number | Site of Ulcer   | Per Cent of Type | Why Operated   | Unsatisfactory Element   |
|--------|---|------------------|--|--|
| 8      | Posterior duodenal  | 16.6             | 4 Pain and hemorrhage<br>3 Pain alone<br>1 Pain and obstruction                | 1 Recur. symptoms when drinking<br>1 Severe anaemia<br>1 Slight pain<br>1 Recur. symptom when emotionally upset<br>3 Slight pain<br>1 Weight loss and weakness |
| 6      | Anterior duodenal   | 22.2             | 3 Pain alone<br>2 Pain and hemorrhage<br>1 Pain and hemorrhage and obstruction | 3 Slight pain<br>1 Weight loss<br>1 Hemorrhage 22 mos. then normal<br>Recur. symptoms with dietary indiscretion  |
| 4      | Duodenal—site unknown   | 44.4             | 2 Pain and hemorrhage<br>1 Pain alone<br>1 Pain and obstruction                | 1 Weight loss and weakness<br>1 Slight pain<br>Slight pain<br>Slight pain  |
| 3      | Marginal ulcer<br>Original site<br>1 Posterior<br>1 Anterior<br>1 Unknown | 27.2             | 2 Pain and hemorrhage<br>1 Pain alone  | 2 Slight pain<br>1 Slight pain   |
| 2      | Gastric   | 13.3             | 2 Pain alone   | 1 Slight pain<br>1 Weakness and weight loss  |
| 1      | Anterior and posterior  | 20.0             | 1 Pain alone   | 1 Slight pain  |

Average period elapsed before recurrence of symptoms 1.2 years.

the site of ulceration and the per cent in which unsatisfactory conditions arose. There is also established herein a direct connection between the precipitating factors of operation and the unsatisfactory sequelae. Since the variance in percentage is so slight and all are in close approximation to the total percents of benefited cases, it would seem that the site of the

TABLE XIII

*Analysis of weight records  
Average pre-operative and post-operative*

Study of all cases showed an average of a fraction of a pound.

47.6 per cent lost weight  
39.2 per cent gained weight  
11.2 per cent remained unchanged  
8.4 per cent more lost weight than gained

ulceration could not be used as a means of prognosticating the outcome of any one case. It is of interest, in reviewing these findings, to note that pain had been a pre-operative finding in every case with an unsatisfactory result. Hemorrhage was a pre-operative finding in approximately the same ratio as it occurred in the entire group.

Weight loss or weight loss accompanied by weakness was present in sufficient numbers to be noticeable. Therefore, a study of the average pre-operative and post-operative weight levels was made on all cases (Table XIII). The findings were somewhat negative inasmuch as the average of the entire group showed a fraction of a pound gain. However, since over eight per cent more patients lost weight than gained post-operatively, serious consideration must be given to

this complaint, even though in our series it was of marked consequence in only four cases.

In many other similar reports authors have given the occurrence of free HCl in any amount and high total acidity levels as a reason for the recurrence of symptoms. In this study (Table XIV) the average post-operative free and total acidity of patients was determined as was also the same findings for the benefited cases.

The findings for the entire group and for cases having recurrent symptoms were very similar. It is of interest to note that 46 per cent of all cases had no free HCl post-operatively, and among these were cases classified as cured, benefited and even unimproved.

By adding the cases classified as "cured" to the

TABLE XIV

*Analysis gastric acidity post-operatively*

|   |
|---|
| 46 per cent had no free HCl post-operatively            |
| Average acidity of patients post-operatively            |
| Free 12   |
| Total 27  |
| Average acidity of the Benefited cases post-operatively |
| Free 11   |
| Total 31  |

group classified as "benefited," it is found that over 90 per cent of the patients who had sub-total gastric resection were helped by this procedure.

3. *Unimproved:* This category included patients who obtained no relief, or who actually became worse, as well as those who experienced recurrence of symptoms in their original intensity. There were nine

TABLE XV  
*Analysis unimproved cases*

| Number | Site of Ulcer                            | Where Operated   | Why Operated        | Unsatisfactory Element  |
|--------|--|------------------|---------------------|---|
| 4      | Anterior duodenal                        | Bellevue         | Pain and hemorrhage | Severe pains recurred in one year.  |
|        |  | Bellevue         | Pain and hemorrhage | Pains and hemorrhage recurred 2½ years also developed P. A.   |
|        |  | Another Hospital | Pain and hemorrhage | Developed marginal ulcers with two perforations. Had second resection now fine.   |
|        |  | Another Hospital | Pain                | Pains recurred immediately after operation.   |
| 1      | Posterior duodenal                       | Bellevue         | Pain and hemorrhage | Ulcer not removed. Pains recurred 3 months. Patient had second operation 2½ years later.  |
| 1      | Posterior duodenal and marginal          | Another Hospital | Pain                | Developed marginal ulcer 3 years later. Had had marginal ulcer following G. E.  |
| 1      | Duodenal—site unknown                    | Bellevue         | Pain                | Would not follow instructions, pains recurred in 8 months. No further follow up.  |
| 1      | Duodenal—site unknown and marginal ulcer | Bellevue         | Pain and hemorrhage | Had G. E. then resection of part of stomach for marginal ulcer. Pains recurred so complete resection of stoma and ¾ of stomach with freedom of symptoms for 2½ years, then death from hemorrhage. |
| 1      | Gastric                                  | Another Hospital | Pain and hemorrhage | Pain recurred four years. Partly controlled by medication.  |

Of 9 unimproved cases 4 or 44.5 per cent were not operated at Bellevue Hospital.

cases, an incidence of 9.2 per cent, in this group. Table XV shows in detail each of these cases. Of the nine unimproved cases, four or 44.5 per cent were not operated on at Bellevue.

In reviewing the unimproved cases, it is found that pain was present as a pre-operative factor in every instance and that hemorrhage was a factor in 7 out of nine cases. Pain recurred in each of these cases while hemorrhage was a recurrent factor in but two cases.

Marginal ulcer, unquestionably the most damaging complication following gastro-enterostomies, occurred in two cases. Both of these patients were operated on in other hospitals. They were operated on at a time when resections were far from sub-total, and in each instance only a small portion of the pyloric end of the stomach was removed. There has never been a marginal ulcer found in any case that we have re-

sected on the Fourth Surgical Division at Bellevue Hospital.

#### SUMMARY

A statistical analysis of 104 sub-total gastric resections for peptic ulcers together with their end results, is presented. Post-operative symptoms do not appear to bear any direct relationship to post-operative complications. Failure to resect an adequate amount of stomach and to remove the ulcer crater is the most common cause for recurrence. Marginal ulcers are not to be feared as a post-operative complication provided sufficient stomach tissue is removed and the ulcer is always removed in toto.

#### REFERENCES

1. Church, Reynold E. and Hinton, J. William: A Study of 671 Cases of Peptic Ulcer with Special Emphasis on 114 Post-Operated Cases. *N. Y. State J. of Med.*, Vol. 34, No. 24, Dec. 15, 1934.
2. Church, Reynold E. and Hinton, J. W.: The Results of Gastro-Enterostomy in Gastric and Duodenal Ulcers. *Surgery*, Vol. 7, 647-656, May, 1940.

## The Obstructed Peptic Ulcer

By

S. ALLEN WILKINSON, M.D.†  
BOSTON, MASSACHUSETTS

THE recognition of pyloric obstruction presents no diagnostic problem but its causation may be obscure and its relief usually raises a nice therapeutic dilemma. Pyloric obstruction as a complication of peptic ulcer occurs in approximately one-tenth of all ulcer cases and in all except the mildest cases demands hospital treatment for its management. It is axiomatic to state that obstruction may be due to spasm or to

cicatricial contraction, but the real test of treatment is the prompt determination of the cause and the application of its proper remedy.

To determine the results of treatment in pyloric obstruction some years after the treatment was instituted, 100 cases treated prior to 1936 have been tabulated. The method of treatment in these cases changed slightly during the years in which they accumulated, but its general principles consisted of bed rest, a bland diet with frequent feedings, the moderate use of

\*Read before the Annual Meeting of the American Gastro-Enterological Association, Atlantic City, N. J., June 8-9, 1942.  
†Department of Gastro-Enterology, The Lahey Clinic.



TABLE I  
*Pyloric obstruction prior to 1936*  
100 cases

| No<br>Recurrence | Recurrent<br>Obstruction | Subsequent<br>Operation | Operation<br>Refused | Not<br>Followed |
|------------------|--------------------------|-------------------------|----------------------|-----------------|
| 20               | 74                       | 35                      | 25                   | 6               |

alkalis with due regard for the all too frequent development of alkalosis, and aspiration of the stomach once or twice daily until the obstruction was relieved or until operation was performed. Many of these patients responded favorably to this regimen while they were hospitalized and they were discharged symptom-free. Some of them remained symptom-free for years (in some cases more than eight years) before obstructive symptoms developed again. Many more, however, showed signs of obstruction as soon as they attempted to reenter active life and were forced to return for operation.

An observation which has been made repeatedly, and

TABLE II  
*Pyloric obstruction prior to 1936*  
Duration of obstruction

|                       | No<br>Recurrence | Recurrent<br>Obstruction | Subsequent<br>Operation | Refused<br>Operation |
|-----------------------|------------------|--------------------------|-------------------------|----------------------|
| Less than<br>3 months | 19               | 10                       | 6                       | 2                    |
| More than<br>3 months | 1                | 64                       | 29                      | 23                   |

TABLE III  
*Pyloric obstruction prior to 1936*  
Division into sexes

|         | No<br>Recurrence | Recurrent<br>Obstruction | Subsequent<br>Operation | Refused<br>Operation | Total<br>Cases |
|---------|------------------|--------------------------|-------------------------|----------------------|----------------|
| Males   | 18               | 51                       | 23                      | 19                   | 74             |
| Females | 2                | 23                       | 12                      | 6                    | 26             |

TABLE IV  
*Obstruction since 1936*  
Results of tube drainage—Non-operated cases

| Case | Duration of<br>Obstruction | Residue in %<br>6 Hours | Tube Drainage in<br>Ounces Per Day | Operation | Recurrence   |
|------|----------------------------|-------------------------|------------------------------------|-----------|--|
| 1    | 6 mos.                     | 90                      | 41-24-18                           | No        | Yes, 1 yr., operation  |
| 2    | 2 mos.                     | Large                   | 34-33-7-2                          | No        |  |
| 3    | ?                          | 25                      | 22-27-35-1-0                       | No        |  |
| 4    | 2 wks.                     | 90                      | 50-42-24                           | No        | Yes, 1 yr., operation refused  |
| 5    | 3 mos.                     | Large                   | 31-34-40                           | No        | Yes, 6 mos., operation   |
| 6    | ?                          | Trace                   | 53-19-18-10                        | No        |  |
| 7    | 10 days                    | Trace                   | 23-22-30-9                         | No        | Hemorrhage, 2 mos., operation  |
| 8    | 4 mos.                     | 50                      | 45-20-4                            | No        |  |
| 9    | 10 mos.                    | Trace                   | 26-22-6                            | No        |  |
| 10   | 2 wks.                     | 10                      | 21-20-9-3                          | No        |  |
| 11   | 2 yrs.                     | 90                      | 44-45-50-41                        | No        | Yes, 3 mos., operation   |
| 12   | 2 mos.                     | 70                      | 24-5-1                             | No        |  |
| 13   | 2 yrs.                     | ?                       | 56-23-31-17-19                     | Refused   |  |
| 14   | 5 mos.                     | 90                      | 20-5-1                             | No        | Yes, 6 mos., operation   |
| 15   | ?                          | 50                      | 10-10-10-4                         | No        |  |
| 16   | ?                          | 90                      | 38-8-7-1                           | No        |  |
| 17   | ?                          | 50                      | 9-1-2                              | No        |  |
| 18   | 5 days?                    | 100                     | 61-89-49-33                        | Refused   | Yes: still obstructed  |
| 19   | 10 wks.                    | Trace                   | 18-3-4                             | No        |  |
| 20   | 2 mos.                     | 100                     | 85-53-40-28                        | Refused   | Perforation—2 yrs.   |
| 21   | 3 wks.                     | 20                      | 13-15-1                            | No        |  |
| 22   | None                       | None (pain only)        | 9-6-9-3                            | No        |  |
| 23   | ?                          | ?                       | 13-18-6                            | No        |  |
| 24   | 3 days                     | Post-op. obstruction    | 23-25-15-12                        | No        |  |
| 25   | 10 mos.                    | Moderate                | 18-11-4-6                          | No        |  |
| 26   | 2 mos.                     | 75                      | 40-36-22-16                        | No        |  |
| 27   | None, pain 3+              | 0                       | 36-30-36-15                        | No        |  |
| 28   | 2 mos.                     | ?                       | 19-15-39-34-20                     | No        | Drainage for post-op. obstruction after gastrectomy for carcinoma of stomach |
| 29   | 1 mo.                      | Large                   | 30-20-9                            | No        |  |

which was stressed by Kiefer (1), is that the duration of obstruction before beginning treatment determines to a large degree the success or failure of medical management. In the cases in which obstruction was present less than three months medical management was most useful, whereas in the group with obstruction for longer than three months recurrences were almost certain in spite of apparent complete relief. In this latter group, operation was deemed necessary most often (Table I).

In the analysis of these 100 cases it is noteworthy that the ratio of males to females is three to one whereas with ulcer in general the ratio is nearer ten to one in this country. More striking is the fact that when the females become obstructed, the probability of recurrence is much greater, ten to one, as compared with a ratio of three to one in the male. From these figures it seems logical to draw the inference that obstruction in the female is of more serious prognostic significance than in the male (Table II and Table III).

Early in 1936 (2) I began to use a method of management of pyloric obstruction which has become increasingly valuable as we grew more familiar with it and its results. This method has been used in more than 100 cases to date at the Lahey Clinic most of which are embodied in the Tables to be presented. Chamberlin (3) has reported on his use of this method in the Army.

The routine of procedure is followed closely in the early stages of treatment and is varied in the later stages in accordance with the patient's progress. As soon after admission as the fact and the degree of obstruction are determined, a Levin tube is introduced into the stomach and the contents of the stomach aspirated. Orders are given to introduce through the tube 3 ounces of a bland, non-curding mixture, such as malted milk made with water, peptonized milk or, in some cases, evaporated milk. With this is included 1 or 2 drams of colloidal aluminum hydroxide. This mixture is given every hour, day and night. For the first thirty minutes of each hour the tube is clamped so that no drainage returns. For the last thirty minutes of each hour the tube is unclamped and the gastric contents are allowed to drain by siphonage into a bottle attached beside the bed, about a foot lower than the level of the patient. This return drainage is measured and the total twenty-four hourly return is charted as a graph on the temperature chart in the same manner that the fluid intake or output might be charted.

At first our chief concern was control of the vomiting and pain. This drainage immediately controls both so that the patient should be comfortable after the first few hours. It was soon observed that there were two general classes of obstruction—those in which the twenty-four hour return drainage fell rapidly to a low

TABLE V  
*Obstruction since 1936*  
*Results of tube drainage—Operated cases*

| Case | Duration | Residue,<br>Per Cent | Tube Drainage in<br>Ounces Per Day | Operation             | Result                                |
|------|----------|----------------------|------------------------------------|-----------------------|---------------------------------------|
| 1    | 3 mos.   | 100                  | 32-25-46                           | Post. gastro-enteros. | Good                                  |
| 2    | 4 wks.   | ?                    | 26-26-30-22-38                     | Post. gastro-enteros. | Good                                  |
| 3    | ?        | 100                  | 26-58-11-60                        | Post. gastro-enteros. | Carcinoma of pylorus, age 46          |
| 4    | 3 mos.   | Large                | 35-40-42                           | Post. gastro-enteros. | Good                                  |
| 5    | 2 yrs.   | 100                  | 33-76-80                           | Post. gastro-enteros. | Good                                  |
| 6    | 4 mos.   | 100                  | 55-65-50                           | Subtotal gastrectomy  | Good                                  |
| 7    | 2 yrs.   | 90                   | 66-74-60-40                        | Post. gastro-enteros. | Good                                  |
| 8    | 8 mos.   | 50                   | 41-11-18-35-31                     | Post. gastro-enteros. | Good                                  |
| 9    | 10 yrs.  | 100                  | 46-20-27-30-25                     | Subtotal gastrectomy  | Good                                  |
| 10   | 1 mo.    | 90                   | 44-42-38-42                        | Subtotal gastrectomy  | Good                                  |
| 11   | 2 mos.   | 90                   | 24-28-31                           | Subtotal gastrectomy  | Good                                  |
| 12   | 2 mos.   | ?                    | 28-22-23-28                        | Subtotal gastrectomy  | Carcinoma of pylorus, age 20          |
| 13   | 1 yr.    | 90                   | 89-115-92-63                       | Subtotal gastrectomy  | Good                                  |
| 14   | 20 yrs.  | 50                   | 45-30-26-15-6                      | Subtotal gastrectomy  | Good                                  |
| 15   | 2 yrs.   | ?                    | 75-45-40                           | Post. gastro-enteros. | Carcinoma of ampulla of Vater, age 31 |
| 16   | 1 mo.    | 50                   | 55-43-40-35                        | Subtotal gastrectomy  | Good                                  |
| 17   | 2 mos.   | 50                   | 24-13-32-28-40                     | Subtotal gastrectomy  | Good                                  |
| 18   | 1 yr.    | Trace                | 20-22-21                           | Subtotal gastrectomy  | Good                                  |
| 19   | 2 wks. ? | Small                | 28-27-20-30                        | Subtotal gastrectomy  | Good; also had obstructive jaundice   |
| 20   | ?        | 90                   | 50-92-107-58-64                    | Subtotal gastrectomy  | Good                                  |
| 21   | 6 mos.   | 90                   | 48-40-36-45                        | Subtotal gastrectomy  | Lymphoma of pylorus                   |
| 22   | 1 yr.    | 100                  | 60-45-30-40                        | Subtotal gastrectomy  | Good                                  |
| 23   | 6 mos.   | 100                  | 70-75-62-50                        | Post. gastro-enteros. | Good                                  |
| 24   | 3 mos.   | 50                   | 30-22-24-26                        | Subtotal gastrectomy  | Good                                  |
| 25   | 6 mos.   | 80                   | 55-57-50-62                        | Subtotal gastrectomy  | Good                                  |

level and those in which there was little tendency for the curve to fall. After a sufficient number of trials it was determined that if the total twenty-four hour drainage fell below 20 ounces per day and remained low, the tube could safely be removed and the patient could resume his usual feedings in normal quantities. In such cases it was felt justified to assume that we were dealing with obstruction due to spasm, and a subsequent review of these cases has verified this conclusion. Table IV shows a summary of a follow-up study in nonoperated cases. In most instances it will be noted that the drainage per twenty-four hours fell to a level lower than 20 ounces by the end of the fourth day and most of such patients have remained well and free of recurrences to date. In the few cases in which the drainage remained above the 20 ounce level, recurrent obstruction occurred fairly promptly in spite of symptomatic relief. Operation was advised at the time in several of this latter group but was refused because of complete freedom from symptoms. Because of these experiences we have established the arbitrary dictum that if the drainage drops below 20 ounces by the end of the fourth day, that patient will do well on medical management and operation will probably not become necessary.

The group of patients who failed to show a falling curve, and whose twenty-four hourly total remained above the 20 ounce mark at the end of the fourth day became or should have become surgical cases. Table V illustrates a group in which operation was carried out. Every one of these had a high curve which did not fall. Three of these patients had unsuspected carcinoma. One case was a lymphoma of the pylorus.

One of the problems faced by the surgeon at the time of operation in these obstructed cases has been the technical management of a dilated, flabby stomach with a thin, more or less atonic, muscular wall. This method of alternate feeding and drainage allows a gradual decompression of a distended stomach so that it returns to its normal size and tone about the fourth or fifth day. By that time the decision will have been made for or against operation. If it is decided that the case needs surgical management, at operation the surgeon finds a stomach of normal size and tone on which to work.

#### SUMMARY

In review of 100 cases of ulcer with obstruction, seen prior to 1936, men predominate over women in a ratio of three to one. Obstruction which has persisted longer than three months is practically certain to recur although the patient may go many years with no sign of trouble. When a woman has obstruction, the hope for ultimate medical cure is much less than with a man, and the chances are ten to one that she will require an operation.

A simple, easily managed procedure for the handling of pyloric obstruction is based on the principle of alternate feeding and drainage so that the stomach never becomes distended and is gradually decompressed. A graphic record of the degree of obstruction and its response to management is obtained and this enables the physician to decide quickly and accurately which cases can best be managed medically and which should come to operation. Finally, those cases which reach the surgeon come to him better nourished, with a better fluid balance and with much improved gastric tone when compared with the group of patients who

have an occasional aspiration or continuous gastric suction for a day or two.

#### BIBLIOGRAPHY

1. Kiefer, E. D.: Personal communication.
2. Wilkinson, S. A.: Medical Management of Pyloric Obstruction. *Surgical Clinics of North America*, 735-741, June, 1941.
3. Chamberlin, D. T.: A Method for Relief of Pyloric Obstruction. *The Military Surgeon*, 90:704-709, April, 1942.

#### DISCUSSION

DR. WALTER L. PALMER (Chicago): Mr. Chairman, I am sure we have all greatly enjoyed these three papers. There isn't very much that I can add to any of them.

Dr. Eusterman didn't have time, I think, to bring out the importance of aspirating the stomach as a check on gastric emptying. If the X-ray seems to show obstruction at the stoma, one may be surprised to find at bedtime that the stomach is nearly empty; on the other hand, the demonstration of a considerable retention confirms the evidence of obstruction.

The last two papers seemed to me to emphasize once again the important fact that there is no absolute cure for this disease, peptic ulcer. The lesion may recur following any type of treatment.

The first part of the paper by Dr. Church and Dr. Hinton emphasized the fact that the longer they followed the patients who had had gastro-enterostomy, the higher the incidence of recurrence. One cannot help wondering if the same may not be true of the patients with sub-total gastrectomy. The greatest disadvantage of the sub-total gastrectomy is not the mortality rate but the fact that when the lesions recur, they are extremely difficult to treat medically and also extremely difficult to treat surgically.

I was surprised to hear Dr. Church say that the location of the ulcer didn't seem to have any bearing on the matter of recurrence. It has been my experience, and I think most of the literature is in accord with the view, that recurrences following resection for gastric ulcer are very rare indeed, that most of the recurrences follow resections for duodenal ulcer, and that these then are the difficult ones to treat.

With regard to Dr. Wilkinson's paper, our limited experiences with intubation have been quite in accord with his experience that if the volume of gastric secretion does not diminish rapidly in the first two days the obstruction is high grade and does not decrease, but if the volume of secretion does diminish rapidly, the obstruction usually responds well to medical management.

The two papers emphasize once more the importance of individualization in treatment. There are, after all, some patients who must be operated on and others who do very well with medical management of the various types.

Thank you.

DR. RALPH COLP (New York): I should very much like to discuss the paper presented by Dr. Hinton and Dr. Church, as far as recurrences following sub-total gastrectomy are concerned:

I could expedite this if I had the first slide.

(Slide) Dr. S. Mage of our staff, made a very careful follow-up study of survivors following operation, of which there were 502, in which a sub-total gastrectomy for a duodenal ulcer was performed. These cases occurred on the services of Dr. Berg, Dr. Lewisohn and mine, and the cases were followed from one to seventeen years.

In the primary cases, of which there were 366, there were 27 so-called recurrences, and the basis for the diagnosis was that the recurrences was proved by operation or post-mortem examination, in six cases, by the characteristic X-ray findings in sixteen, and by gross bleeding in five in which there was no apparent X-ray evidence of ulceration, and yet we felt this bleeding must be ascribed to some recurrent type of either ulcer or ulceration.

In the secondary group of 138 cases, there were thirteen recurrences, seven proven by operation or post-mortem.

four demonstrated by X-ray, and two in which gross bleeding was evident, so that in the total of 502 cases there were 40 recurrences.

In all the cases, a sub-total gastrectomy of the Billroth II type was done, applying the DePetz clamp well proximal to the reentrant angle removing about three-quarters of the stomach. We do not perform partial gastrectomy: we perform a sub-total gastrectomy, and I want to emphasize that point very definitely. In the gastric ulcer cases of which there were 92, there was only one recurrence. This emphasizes the point which Dr. Palmer has made, that these patients following a sub-total gastrectomy for gastric ulcer, invariably have an anacidity. Whereas according to the studies of Dr. Winkelstein, in cases of duodenal ulcer, in which a sub-total gastrectomy was performed, fully 50 per cent of these patients have acid. If they have acid, they are potential candidates for recurrent ulceration.

(Slide) When it comes to percentages, we find there was a 6.1 per cent recurrence as proven by operation and X-ray in a total of 502 cases of duodenal ulcer for which a sub-total gastrectomy of the Billroth type was performed. If those cases which presented in addition to operation and X-ray, evidences of gross bleeding are added, the percentage becomes a little higher, 8 per cent. In gastric ulcer cases, the percentage of recurrence was very low; 1 per cent.

Dr. Church mentioned that he felt the actual removal of the ulcer crater is an important factor in diminishing the recurrences following sub-total gastrectomy. In forty of these cases, recurrent cases, Dr. Mage went over the specimens and found in 33 of the 40 that the ulcer had been removed. We feel quite definitely that the removal of the ulcer has very little to do with the recurrence.

How, then, are these recurrences to be explained? As I stated before, we feel if an anacidity is achieved, the incidence of recurrence is going to be minimal. If you have free acid present after operation, incidence of recurrence is going to be much greater. Most of these recurrences occurred within the first two years, yet recurrences occurred as late as twelve years after the sub-total gastrectomy. This means that the cases must be followed indefinitely.

However some of these cases, regardless of the extent of resection, regardless of the size of the stoma and the neutralization caused by regurgitation of the alkaline duodenal contents, will have free acid. They, to me, represent a group in which the tendency to recurrent ulceration is almost "malignant." In these the prognosis is as bad as in gastric carcinoma. For even if you resect these patients again and again, they may develop a recurrence as long as they possess a segment of stomach.

Thank you, sir.

DR. ASHER WINKELSTEIN (New York): Mr. Chairman and Friends: It is the purpose of my discussion to emphasize some of Dr. Colp's points and to add a few additional observations.

We have had a personal follow-up of the partial gastrectomy patients at The Mount Sinai Hospital for seventeen years. These patients were operated on the services of Drs. Berg, Lewisohn, and Colp. We have arrived at certain conclusions which we have previously presented before this Association and which we wish to emphasize again.

We have concluded that partial gastrectomy for gastric ulcer at the incisura angularis produces in practically 100 per cent of the cases an achlorhydria. I should like to ask Drs. Hinton and Church what their experience has been in this group. We consider this post-operative achlorhydria a *sine qua non* for the surgical cure of ulcer.

In partial gastrectomy for duodenal ulcer, however, the situation is different. A post-operative achlorhydria occurs only in 55 per cent. In the 45 per cent which still have free acid post-operatively, one sees a considerable number of recurrences. However, the per cent of recurrences is

only approximately one-third of what one sees after gastro-enterostomy for duodenal ulcer.

We have noted that these ulcers after partial gastrectomy for duodenal ulcer occur in the group of patients who have a very high pre-operative acidity. A few years ago Dr. A. A. Berg and I presented before this Association the idea of adding anterior subphrenic vagotomy to the operation of partial gastrectomy in duodenal ulcer patients with a very high pre-operative acidity. This procedure has been carried out in a fairly large group on the services of Drs. Berg and Colp. It produces a post-operative achlorhydria in most of the duodenal ulcer cases. I would like to urge the surgeons to add this simple surgical procedure in that type of case. Also, at my suggestion, high anterior subphrenic vagotomy plus gastro-enterostomy has been used in a selected group of patients with duodenal ulcer. The results have been encouraging and warrant further trial.

DR. HENRY A. RAFSKY (New York): Dr. Eusterman's timely paper is certainly of interest to those of us who do gastroscopy, because the gastroscopic and X-ray findings do not always tally. I think this paper will aid in solving this problem. In reference to Dr. Wilkinson's paper I wish to state that it is important, in cases of pyloric obstruction, to differentiate between a cicatricial pyloric stenosis and an inflammatory pyloric occlusion. This cannot always be done by clinical and roentgenographic findings. The therapeutic test must often be the final judge. The inflammatory type will respond to medical treatment and the cicatricial type should be operated upon. I have, upon a previous occasion, reported the fact that the medical treatment of these patients does stand the test of time. It should also be borne in mind that a pronounced degree of pyloric obstruction does not necessarily mean that the patient must submit to surgery. A man of thirty-seven who was first treated by me in 1926, had a forty-eight hour retention when he was first seen. He was successfully treated. A woman of fifty-seven had a seventy-two hour retention when she was first observed. It is now almost nine years and she has not had a recurrence of symptoms. I would like to show a slide to demonstrate a method which we employed, in the hospitalized patients with pyloric obstruction, to determine whether medical treatment would be feasible. This procedure was originally described by Dr. Einhorn. A duodenal tube, with a bead and string attached, are introduced. As the edema subsides the bead goes through the pylorus and as the edema further subsides, the tube enters the duodenum. Duodenal feedings are then instituted. The advantages of this method are that not only can you treat the patient medically if the tube passes the pylorus but also that, if it does not enter the duodenum in five to seven days we know that we are dealing with a cicatricial stenosis and that the patient is not likely to get well on medical treatment.

DR. FRANKLIN HOLLANDER (New York): Dr. Church and Dr. Palmer have both commented upon the fact that the longer a group of cases is followed, after a sub-total gastrectomy for ulcer, the greater will be the incidence of failure observed for that operation. With this idea in mind, Dr. McGee, to whom Dr. Colp referred before, and I have attempted to develop a statistical technique rather different from any of those in general use. We needed to develop a technique which would enable us to plot a time curve for the development of recurrences following this particular operation, and, without going into any of the details, I should like to give you a brief idea of what that technique is because we feel it is fundamental to any study on this subject such as Dr. Church has presented.

The end result of our technique is a curve in which we plot on the horizontal axis the number of years following the application of this particular operation to a large

group of cases, where the cases have been operated on in different years, and they are grouped in such a way that the comparison is made on the basis solely of the number of years following operation.

In that way we avoid the difficulty which arises from an average period of follow-up, you observe. In one group of cases that we have been able to follow from Dr. Bergh's old service for a period of sixteen or seventeen years, we have plotted our curve from the first through the seventeenth year post-operative and, on the vertical axis, we plot the cumulative percentage of recurrence; that is, any point on this curve gives us the total percentage of recurrence in this group from the time the cases were operated on up through the year of observation; hence, the cumulative element in the study, and we find in general that we get a curve of this particular type.

If we focus attention for the moment on the five, ten, and seventeen-year periods, we find our curve rises more or less steeply during the first five years of follow-up. During the second five years of follow-up, it falls off appreciably; as a matter of fact, the height, the percentage incidence of the curve, for the ten-year period, is just one and a half times that for the five-year period and, after ten years the curve remains horizontal in this particular group of cases; in other words, all of the recurrences which could possibly develop have developed in this by the tenth year.

We have another set of cases operated on by Dr. Bergh in which we could do only an eleven-year study, and here we find that the curve has very much the same shape. It rises to a value a little lower than in our first sample, rises again at a somewhat slower rate to a value which is only 50 per cent higher than this, and then tends to remain horizontal. Whether it will continue to remain horizontal without further increases, we can't say at this time.

We have a third group of data followed for only six years and therefore we do not feel that they tell us much about the picture.

We feel that the question of statistical methodology in these cases is very much more important than ordinarily thought, and we hope to present the details of our technic at the meeting next year.

DR. A. F. R. ANDRESEN (Brooklyn, N. Y.): We have listened to a very interesting symposium and although the time is late I believe that two important points should be emphasized:

In the first place, it is to be remembered that where a gastro-enterostomy is unnecessary, that is, where there is no obstruction to gastric emptying, or where a temporary obstruction clears up after operation, the new stoma is liable not to function properly or even not to function at all, eventually often becoming completely closed. This is the most frequent answer to the many cases of malfunctioning and closed stoma after gastro-enterostomy, although of course faulty technique or improper choice of operative procedure may also be factors.

In the second place, with improvement in the technique of partial gastrectomy, the operative mortality has decreased to such an extent that it is to be feared that many of these operations are performed unnecessarily. It has been mentioned that in a series of sub-total gastrectomies persistent pain was the most frequent indication for operation. It is certainly unjustifiable to perform such an elaborate mechanical procedure for a mere symptom, without taking into consideration the causes of the pain. Persistent pain may be due to a great variety of causes, some mechanical, many functional. If the persistence is due to the ulcer being complicated by obstruction due to scars or adhesions causing deformities and narrowing, it requires operation. If due to a partial or walled-off perforation adherent to neighboring organs, we have another indication for operation, and if the ulcer is really a carcinoma, early operation is certainly indicated. But if persistence

of pain is due to irritation of the ulcer area as a result of disease elsewhere, either within or without the gastrointestinal tract, to toxic, endocrine or neurological disturbances, to nutritional deficiencies as a result of ill-advised and too restricted diets, or to irritation from certain elements of the diet or medication, as in allergy, operation is certainly contraindicated. In milk allergy, the removal of milk from the ulcer diet will often accomplish really remarkable results.

I wish to give a warning against using a mechanical procedure to treat a non-mechanical symptom like pain, and to plead for careful and repeated study of patients with persistent ulcer symptoms in order to determine their cause.

DR. GEORGE B. EUSTERMAN (Rochester, Minn.): I am not in agreement with Dr. Andresen's observations concerning these patients. The fact remains that the great majority of these patients had a chronic peptic ulcer pre-operatively, and this is true of the great mass of patients with ulcerative or inflammatory lesions of the gastro-enteric stoma. I should like to comment on Dr. Church's paper by saying that in addition to recurrent ulceration and diffuse gastritis, often of a very refractory nature, it is not uncommon to encounter severe nutritional disturbances in a patient whose stomach has been resected. As regards the last mentioned complication, we are completing a piece of research which has yielded some very important information.

Dr. Wilkinson's paper is important and timely. The fact that pyloric obstruction in the female implies a poor prognosis from a non-surgical standpoint, in the essayist's experience, is highly instructive, and as I look back on my own experiences I am inclined to wholeheartedly agree with him. On the other hand, post-operative recurrences of the type such as I have discussed, occur much more frequently in the male than in the female.

The question of duration of obstruction is interesting. It has been my experience that it is sometimes difficult to determine even with any degree of assurance just when such obstruction has taken place. Patients occasionally have marked obstruction without the usual symptoms, and the only sign may be that of a succession splash.

Regarding Dr. Hollander's observations, it has been my experience that the symptoms of jejunal ulcer, or its equivalents, occur in the large majority within a period of a year after operation. Of course, one can only speculate as to the cause of recurrence at the gastro-enteric stoma but it is reasonable to presume that a high acid titer, with hyperplastic mucosa, poor choice of patients and poor technic, play an important contributing, if not actually a primary role.

REYNOLD E. CHURCH (New York): I wish to thank those who discussed our paper. We agree that the length of Follow-up is a very important factor if an attempt is to be made to evaluate End Results. We have followed cases since 1933 with an average follow-up period of 2.88 years. With a longer period we expect to find more failures and more cases transferred from cured to benefited rating.

In abstracting a paper to a period of ten minutes it is impossible to give all the facts in the paper. I did not mention that 89 per cent of the cases were operated at Bellevue Hospital and 11 per cent elsewhere. I did not mention that the operation as we perform it now is the Moynihan anterior anastomosis with a removal of at least 65 per cent of the stomach.

I agree with Doctor Colp and his confreres that it is essential to remove a large part of the stomach if you expect to get results.

I was asked a direct question as to the post-operative acidity in gastric cases. I think you will recall from our study there were not many gastric cases and therefore I think from that number we would be in error in trying

to derive too many conclusions. It is true that gastric cases do have a much lower acidity post-operatively.

No attempt is made to describe why the failures occurred in gastric cases. I do not know why they occur but the results as we interpret them show they do.

We were greatly surprised to find the number of anterior ulcers that were present in this series. Certainly our feeling at the present time is that we are operating on practically all posterior ulcers. We believe this has a great deal to do with the question of pain, for we believe it is the induration and involvement of the pancreas or a neighboring viscus that accounts for the pain.

It is not our policy to operate on cases for the symptom pain alone. All cases are adequately treated by medical means and then if pain persists we believe it is due to involvement of a nearby structure.

DR. SAMUEL A. WILKINSON (Boston, Mass.): With reference to Dr. Eusterman's comment in regard to the duration of obstruction, it is difficult in many cases accurately to estimate the duration but an approximation can be made in most cases. If the patient gives a history of

having vomited intermittently but persistently once a week or more often for the past several months, I consider that the patient has been obstructed at least partially for that length of time. If he comes with no history of vomiting or obstruction and, as we often find, the X-ray discloses a dilated and distended stomach with a large residue, we consider him just as much obstructed as the person who has a long history but our use of the duodenal tube has been able to convince us that this obstruction is usually due to spasm and will respond to the method of drainage treatment fairly quickly and also this person is less apt to have a recurrence than the chronic vomiter with obstruction.

It is important to stress the fact that the drainage should be collected and charted at regular intervals. We ask our nurses to chart the drainage from the tube on the front of the clinical chart, exactly as one would chart urinary intake and output, using a distinctive color. By this means, we can look at the chart and gain a quick estimate of the exact progress of the drainage.

## A Summary of Preventive Methods in Certain Tropical Diseases

By

Z. BERCOVITZ, M.D.\*  
NEW YORK, NEW YORK

THE object of this paper is to present some of the known facts regarding preventive methods in certain tropical diseases. Because of the lack of time it will be impossible to review the literature and give the experimental data upon which the conclusions are based.

### MALARIA

Quinine and atabrine are the drugs most commonly employed at the present time in the treatment and prevention of malaria. These drugs are not true chemoprophylactic agents in the sense that they will prevent infection. Both quinine and atabrine are effective against the asexual cycle of the malarial parasite in man and thus are of value in reducing the parasitic index, the case rate and relapse rate of malaria.

The prophylactic dosage of quinine is 0.65 grams (10 grains) taken each evening at bed time while the person is in the infected area and for a period of 8 weeks after leaving that district. At times quinine causes disagreeable symptoms and it has been found that a satisfactory substitute method is to give the dosage of quinine for 7 days alternating with a period of 5 days during which no quinine is administered.

The dosage of atabrine when used as a prophylactic drug is 0.1 grams (1½ grains) given as a tablet 3 times weekly during the period of stay in a malarial district. For short periods of time when in an area heavily infected or in which a severe form of malaria is present in epidemic form atabrine may be administered in dosage of 1 tablet (0.1 grams) daily. At times the drug causes some yellowish discoloration of the

skin due to deposit of the pigment of the drug in the skin but this disappears in a short time after withdrawal of the atabrine. It is not associated with any toxic manifestations involving the liver or kidneys. There have been no untoward effects as a result of prolonged administration of atabrine in the dosage of 1 tablet (0.1 grams) 3 times weekly over a period of 5 years in a number of persons under my supervision in the heart of Africa and in South America. Reports during this period indicate that they have been well and without any malarial attacks. Reexamination of members of this group has shown the blood to be free from parasites and the patients physically in good condition. In a recent case 1 tablet of atabrine was given daily for 4 weeks without any ill effect.

As a result of the review of the literature comparing atabrine and quinine prophylaxis during the past 8 years it was found that under atabrine there was a lower parasitic index, lower case rate and lower relapse rate.

It is of greatest importance to remember that neither atabrine nor quinine in prophylactic dosage will prevent infection with certainty or sterilize the blood of malaria parasites after infection has taken place. As a result of the effect of these drugs on the asexual cycle the number of parasites in the circulation may be reduced to such an extent that it may be difficult or impossible to find them in thick or thin films. Unless antimalarial therapy is continued for a sufficiently long period of time after leaving the malaria district clinical malaria may develop in that person. Quinine in the dosage of 0.65 grams (10 grains) must be continued for at least 8 weeks or atabrine 0.1 grams (1½ grains) daily for at least a month. Even under these conditions relapses may occur and the patient should keep in touch with his physician. In spite of these imperfections both quinine

\*Physician-in-charge Parasitology Service—Bureau of Laboratories, Department of Health, City of New York, Assistant Clinical Professor Medicine, New York Post-Graduate Medical School and Hospital (Columbia University) New York, N. Y.  
Read at the Annual Meeting of the American Gastro-Enterological Association at Atlantic City, N. J., June 8, 1942.



and atabrine are of value in maintaining a person free from clinical malaria while in the tropics.

### YELLOW FEVER

As a result of the work carried on by the Rockefeller Foundation over a period of years it has been demonstrated that vaccination against yellow fever can be carried out on a large scale. The following information is quoted from a form letter from the Chief of the Bureau of Medicine and Surgery of the United States Navy published in War Medicine, Vol. 1, page 429.

"The yellow fever vaccine is prepared by the laboratories of the International Health Division of the Rockefeller Foundation, New York. It consists of a special strain of living yellow fever virus which has been attenuated through prolonged cultivation in tissue cultures. The material is placed in ampules and is then rapidly frozen, desiccated, sealed and stored at a temperature not higher than 4° C."

"The vaccinating dose is 0.5 cc. of an approximately 1:10 dilution of the concentrated vaccine."

"After an ampule has been diluted, any vaccine which remains unused after three hours will be discarded."

"Yellow fever vaccine should not be given concurrently with small-pox vaccine. When both vaccinations are to be made it is suggested that yellow fever vaccine be given first and at least five days elapse before the small-pox vaccination is made. There is no objection to the simultaneous administration of yellow fever and triple typhoid vaccine or toxoid."

"A very mild reaction may occasionally be noted four to seven days after the injection, but the reaction is so mild it seldom interferes with routine duties."

"Present studies indicate that immunization against yellow fever by this method is of lifelong duration, but in the presence of an epidemic another dose is given."

### TYPHUS FEVER

Vaccination against typhus fever is summarized in circular letter No. 3 of January 14, 1942, by the office of the Surgeon General of the United States Army and published in War Medicine, Vol. 2, January, 1942, as follows:

"At present the approved vaccine consists of a suspension of killed, louse-borne, epidemic typhus rickettsiae prepared by the Cox yolk-sac culture method."

*"Initial vaccination.* This will consist of three injections of the vaccine, 1 cc. each, administered subcutaneously, with intervals of from seven to ten days between injections."

*"Subsequent vaccinations.* A stimulating dose of 1 cc. of typhus vaccine may be administered every four to six months as long as serious danger of infection is present. Other 1 cc. doses of typhus vaccine may be given whenever in the opinion of the surgeon this additional stimulation of immunity is indicated."

### CHOLERA

Prophylactic methods against cholera include the use of cholera vaccine. Quoting again from the same

letter of the Surgeon General as published in the same issue of War Medicine:

"The vaccine now approved consists of a suspension of 8,000 million of killed cholera vibrios (V. comma) per cubic centimeter."

*"Initial vaccination.* This will consist of two subcutaneous injections of cholera vaccine with an interval of from seven to ten days between the injections. The first dose shall consist of ½ cc. and the second dose shall consist of 1 cc. of the vaccine."

*"Subsequent vaccinations.* A stimulating dose of 1 cc. of cholera vaccine may be administered every four to six months as long as serious danger of infection is present. Other 1 cc. doses of cholera vaccine may be given whenever in the opinion of the surgeon this additional stimulation of immunity is indicated."

In addition to the work with vaccines considerable work has been done by Morrison and his associates in the control of cholera in India by the use of bacteriophage. The reports are of interest and stimulating of thoughtful consideration but so far most competent bacteriologists are inclined to reserve final judgment until more data is assembled.

### AMOEBIC DYSENTERY

Colonel Charles F. Craig has suggested that Diodoquin may be of value as a prophylactic agent against amoebic dysentery. In Colonel Craig's opinion the use of 7 tablets daily for 20 days as used in the treatment of chronic amoebiasis would be adequate protection against infection with amoebae such as would come through food or drink during the period of drug administration.

During the past year, the author has seen a number of persons from Africa, South America and Central America who have been in the habit of taking from 1 to 3 tablets daily of chiniofon at the onset of an attack of diarrhea and continuing this dosage as long as treatment symptoms were present. These persons stated that this has controlled the clinical symptoms and examinations of stools after return to this country have failed to reveal infection with *Endamoeba histolytica*.

There is no contraindication to the use of either diodoquin or chiniofon in dosages as outlined above and the use of these drugs under those conditions should be encouraged. It may be these agents will prove of value in preventing bacillary dysentery.

### BACILLARY DYSENTERY

The problem of vaccination in bacillary dysentery has been studied for many years and so far no satisfactory vaccine has been developed. A fairly large literature has accumulated regarding the use of bacteriophage and the experience in Brazil, Egypt, Russia, France and Germany indicate that morbidity may be reduced by the oral administration of polyvalent dysentery bacteriophage whenever an outbreak begins. The oral administration of phage in the early stages of a dysentery is harmless and a careful study, well controlled, should be made. There is no contraindication to giving polyvalent dysentery phage in the face of an epidemic outbreak of bacillary dysentery.

### AFRICAN SLEEPING SICKNESS

There is some evidence to warrant the suggestion that a single injection of 1 gram of Bayer 205 will give protection against the trypanosomes causing this disease. It is said to be effective for a period of 3 or

4 months and possibly longer. Whenever traveling in a sleeping sickness area it is important to avoid places where the tsetse flies are prevalent and also to wear long trousers to protect the legs and ankles for the flies have a tendency to bite in these parts.

## Metabolic Disturbances in Workers Exposed to Dinitrotoluene\*

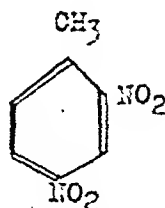
By

LEMUEL C. McGEE, M.D., Ph.D.  
WILMINGTON, DELAWARE  
ALEXANDER McCausland, M.D.  
BLACKSBURG, VIRGINIA  
C. A. PLUME, M.D.  
SUCCASUNNA, NEW JERSEY  
and  
N. C. MARLETT, M.D.  
BELVIDERE, N. J.

**D**INITROTOLUENE poisoning was recognized as early as 1909. Friedlander at that time described dinitrotoluene intoxication in a factory worker (1). He noted also the accentuation of symptoms following the drinking of beer by the workman. The toxicity of dinitrotoluene to workers exposed to it in the manufacture of munitions was not generally recognized until World War I (2, 3, 4, 5, 6). During peacetime enterprises, there is little opportunity for clinical observations of the effects of this and related aromatic nitro compounds on man. This is due to the fact that, in the absence of war, (a) there are fewer men exposed, and (b) those who are exposed have had prolonged training in the proper technical handling of the materials. It is the purpose of this report to present certain observations made on a selected group of 154 workers who have had close contact with dinitrotoluene for the first time during the past year. These workers were not engaged in the manufacture or purification of the compound but were engaged in its application to the manufacture of military powders. In the latter operation, the chief exposure to dinitrotoluene (confirmed by experience of the supervisors, the industrial physicians and the air analyses of safety engineers) occurs in two places, designated as the "D.N.T. Screening House" and the "Coating House."

Last year a review of the aromatic amino and nitro compounds, their toxicity and potential dangers, was published by von Oettingen (7). His report should be consulted for a comprehensive summary of published medical experience with these compounds.

The dinitrotoluene to which the group of workers studied were exposed is primarily the 2-4 form:



2-4 di-nitro-l-toluene

In the crystalline state it appears as fine, light yellow needles which tend to agglutinate into lumps of varying size. The melting point of 2-4 dinitrotoluene is 69.5-70.5 C., the boiling point is 300 C. (with slight decomposition.) The compound is insoluble in water, slightly soluble in ethyl alcohol and quite soluble in diethyl ether. The commercial dinitrotoluene used in smokeless powder manufacture has a melting point near 65.5 C., which would indicate the presence of lower melting isomers in significant amounts. In the experience of the French, twenty-five years ago, the 2-6, 2-5 and 3-4 isomers appeared to be the chief cause of poisoning in munition workers (3). These isomers are formed in the nitration of toluene to the dinitro stage and, having a melting point of from 64 to 50 C. and lower, are found primarily in the oily portion of 2-4 dinitrotoluene when purification is not complete.

It is assumed, on the basis of experience, that dinitrotoluene reaches the body by, (a) inhalation of the vapor of the oil remaining in the crystalline material (chemists state that the vapor tension of the dinitrotoluenes at room tension is quite low. It is sufficiently appreciable to be recognized in a workroom by its odor); (b) inhalation of dust particles of dinitrotoluene; (c) ingestion of food contaminated by soiled hands (a result of needlessly poor personal hygiene); (d) absorption through the skin (3).

### OBSERVATIONS

One hundred and fifty-four men exposed to dinitrotoluene in screening houses and coating houses form the basis of this report. One hundred and twelve of this group reported complaints on one or more examinations. There were 42 of the total group of workers who at no time during the twelve-month period of our observations reported symptoms of feeling unwell. Four of the group of 42 workers developed an anemia without other signs of illness. There was objective evidence of sickness during one or more examinations in 84 employees of the total group exposed. There were 32 workmen who presented complaints without having objective evidence of intoxication or illness. There were two instances of acute toxic hepatitis with jaundice. Both were mild in character. No workman

\*Read at the Annual Meeting of the American Gastro-Enterological Association at Atlantic City, N. J., June 8, 1942.

was so seriously affected as to require hospitalization.

The symptom most frequently encountered, in our experience, was that of an unpleasant taste in the mouth. The description of the gustatory sense varies, but is most likely to be described as metallic or mildly bitter in character. This was followed closely in frequency by sensations of muscular weakness, headache (mild to severe, intermittent or continuous), a loss of appetite, and sensations of giddiness, dizziness or drunkenness. Workmen suffering from dinitrotoluene intoxication also had nausea and vomiting, difficulty

TABLE I

*Symptoms presented by 154 dinitrotoluene workers*

| Symptom                             | Screening House No. of Workmen | Coating House and Air Dry No. of Workmen | Total  |          |
|-------------------------------------|--------------------------------|--|--------|----------|
|                                     |                                |  | Number | Per Cent |
| 1. Unpleasant taste in mouth . . .  | 62                             | 34                                       | 96     | 62%      |
| 2. Weakness . . .                   | 51                             | 27                                       | 78     | 51%      |
| 3. Headache . . . .                 | 48                             | 28                                       | 76     | 49%      |
| 4. Inappetence . .                  | 42                             | 30                                       | 72     | 47%      |
| 5. Dizziness . . . . .              | 49                             | 25                                       | 68     | 44%      |
| 6. Nausea . . . . .                 | 39                             | 18                                       | 57     | 37%      |
| 7. Insomnia . . . . .               | 37                             | 20                                       | 57     | 37%      |
| 8. Pain in extremities . . . . .    | 26                             | 14                                       | 40     | 26%      |
| 9. Vomiting . . . . .               | 22                             | 13                                       | 35     | 23%      |
| 10. Numbness and tingling . . . . . | 18                             | 11                                       | 29     | 19%      |
| 11. Loss of weight (5 lbs. or more) | 7                              | 3  | 10     | 6.5%     |
| 12. Diarrhea . . . .                | 3                              | 5  | 8      | 5.2%     |

sleeping during off hours, and suffered from pain, numbness and tingling sensations in the extremities. The discomfort in the extremities was occasionally localized about joints, at times limited to one extremity and one joint. A loss of weight was uncommon, possibly because of the carefulness with which the health of these workmen was followed. Our experience with these men during the past twelve months does not lend itself to an analysis for the influence of the seasons on the incidence of complaints. The symptoms described by these workers are presented in Table I.

The chief findings from clinical examination of intoxicated workers were pallor, cyanosis and anemia (Table II.) Both pallor and cyanosis of marked degree may be present in workmen particularly sensitive to dinitrotoluene without a significant change in the blood counts. This was notably true of workmen who developed signs and symptoms the first, second or third day of exposure. An occasional workman was so highly sensitive to exposure to dinitrotoluene that acute symptoms of illness, together with cyanosis, appeared after but a few hours of work. The low incidence of leukocytosis and leukopenia suggests that alterations in the leukocyte count early in intoxication is of doubtful significance insofar as dinitrotoluene is concerned. Workmen not exposed to dinitrotoluene

have had leukocyte counts showing about the same frequency of variation from week to week (above 12,000 or below 5,000) from incidental intercurrent infections. In individual case histories the leukocyte count remained high with no apparent cause other than the prolonged exposure to dinitrotoluene. Twenty-three of the 36 anemias (60%) were of the hyperchromic, macrocytic type. The remaining 13 were either normocytic-normochromic or slightly hypochromic in character.

The symptoms of beginning intoxication disappeared rapidly (two or three days) after removal of the workman from his exposure. In many instances the workman recovered from minor symptoms appearing upon his first experience with dinitrotoluene without his removal from that industrial operation. Cyanosis and pallor disappeared within a day or two after the subject was transferred out of exposure. Where anemia had developed (below 13.6 gm. hemoglobin and 4,000,000 erythrocytes) it was observed that the count and hemoglobin value returned to normal slowly. With presumably adequate doses of ferrous sulphate a normal blood count was often not regained for more than two months after removal from exposure. The use of crude liver extract given with the iron medication shortened this time approximately by half.

Schwartz has called attention to instances of dermatitis due to sensitivity of the skin to dinitrotoluene (8). There were 6 instances of dermatitis attributable to dinitrotoluene (after investigations which included patch testing) in the group of workmen considered in the present report.

TABLE II

*Findings in 154 dinitrotoluene workers*

| Finding                           | Screening House No. of Workmen | Coating House No. of Workmen | Total  |          |
|-----------------------------------|--------------------------------|------------------------------|--------|----------|
|                                   |                                |                              | Number | Per Cent |
| 1. Pallor                         | 40                             | 15                           | 55     | 36%      |
| 2. Cyanosis                       | 38                             | 14                           | 52     | 34%      |
| 3. Anemia                         | 28                             | 8                            | 36     | 23%      |
| 4. Leucocytosis                   | 12                             | 7                            | 19     | 12%      |
| 5. Hypotension                    | 8                              | 1                            | 9      | 5.8%     |
| 6. Skin rash                      | 2                              | 4                            | 6      | 3.9%     |
| 7. Leucopenia                     | 2                              | 3                            | 5      | 3.2%     |
| 8. Acute toxic hepatitis—jaundice | 1                              | 1                            | 2      | 1.4%     |

### CASE REPORTS

The experience of two men who developed jaundice is summarized in the following case reports:

Case 1 is a single, white male of 20 years. He began work June 25, 1941, as a D.N.T. Screen Operator. There was no history of previous jaundice, anemia or other illness which might make him unduly susceptible to toxic chemicals. He had had poison ivy dermatitis. His blood pressure June 25 was 130/78 with pulse of 80. His liver was barely palpable at the costal border. A blood count showed 4,950,000 erythrocytes with 15.6 grams of hemo-

globin and 7,800 leukocytes. A blood Kahn test was negative and the urinalysis was unchanged.

His work in the D.N.T. Screen House was to pulverize lumps of dinitrotoluene by means of a paddle. He performed this work from June 25 to July 31, alternating one week in and one week out of the exposure. He did not report for medical examination until July 31, reporting then only because he felt unwell.

On that date he complained of headache, insomnia, weakness, nervousness, loss of appetite, nausea and vomiting, an unpleasant taste in his mouth, and pains in both legs. He was pale, his lips and finger nails were blue, and there was a slight yellow tinge to the sclerae. His liver was palpable two fingers breadth below the costal margin and was tender. His urine was dark but showed no other change. A blood examination revealed 3,070,000 erythrocytes and 12.75 grams of hemoglobin. The blood smear was that of a hyperchromic macrocytic anemia. His treatment consisted of permanent removal from dinitrotoluene exposure, 20 grains of ferrous sulfate daily, and a high carbohydrate, low-fat diet. Liver extract was given intramuscularly at three day intervals. Sodium bromide and tincture of belladonna were administered for the first few days to relieve nausea. After forty-eight hours all symptoms and the faint yellow tinge of the sclerae disappeared.

On August 8, his erythrocyte count was 3,810,000 with 12.7 grams of hemoglobin. His liver was still slightly palpable, but was not tender. By August 15, the liver was no longer palpable. His blood count September 12 showed 5,650,000 erythrocytes and 18 grams of hemoglobin. He has remained well, and has had neither symptoms nor complaints on subsequent examinations.

Case 2 is a single, white male of 22 years. He was examined June 7, 1941, as a prerequisite to his entering dinitrotoluene exposure. He gave no history of previous illness other than one attack of bronchial asthma several years before. He presented no abnormalities on physical examination. His blood Kahn was negative. His blood counts and urinalysis were normal.

On the day following this examination, he began work in a building where powder grains are coated with dinitrotoluene in a revolving drum. Exposure in this operation comes largely through breathing vapor and dust when the drums are opened. The employee continued to work at this job for three weeks without reporting for medical examination.

He came to the medical unit July 1 with complaints of inappetence, an unpleasant taste in his mouth, nausea, dizziness, nervousness and pains in his left arm. His pulse rate was 80 and blood pressure 138, 80. There was slight pallor of his face, cyanosis of his lips, ear lobes and finger nails, and a perceptible yellow tinge to the sclerae. His liver was palpably enlarged and tender. His urine was dark in color and showed an occasional erythrocyte on microscopic examination. The plasma icteric index was 18.5. His blood count showed 5,200,000 erythrocytes with 17 grams hemoglobin and a normal leukocyte count.

In addition to removal from exposure, his treatment consisted of ferrous sulfate, liver extract, sedation for nausea and nervousness, and a high carbohydrate diet. On July 3 his plasma icteric index was 17.5. His symptoms were somewhat diminished; his liver was still tender. By July 9 he was symptom free. His liver was no longer tender but was still palpable. A blood count showed 4,650,000 erythrocytes and 16 grams of hemoglobin. On July 11 his icteric index was normal, and his liver was not palpable.

At the time of his examination February 10, 1942, this worker had gained five pounds in weight. No evidence of residual physical impairment could be found.

In the first case history, there was evident acute damage to the hemopoietic system. The jaundice may have been due to increased bilirubin liberation in part as well as to acute hepatitis. In the second case, it is noteworthy that there was not sufficient blood destruction to cause an anemia. There was clinical evidence of acute liver and kidney damage; neither was permanent. These two workmen represent the most serious poisoning seen by us as a result of dinitrotoluene exposure. Both experiences occurred early in the training of these operators. The fact that they failed to report to the medical department as frequently as they were instructed to do, is probably significant.

#### INFLUENCE OF ALCOHOL

The medical supervision of munition operators affords an opportunity to note the additive or contributory influence of other toxic agents upon the effects of exposure to dinitrotoluene. It was common experience in World War I that habitual users of alcoholic beverages did not tolerate exposure to toxic chemical compounds as well as did workmen who abstained from alcohol.

The workmen considered in the present report were interviewed in the plant medical unit weekly or bi-weekly with the exception of a few men (see case reports) who, due to misunderstanding or improper control, missed such examinations early in their work. During these examinations, each man was questioned carefully as to his use of alcoholic drinks (including beer) and their effects since he entered the dinitrotoluene operations. Of the group of 154 men, 23 described a reduced tolerance for alcohol and 31 stated that their symptoms had been aggravated by taking alcohol. Some workers reported that they had found it impossible to drink any alcoholic beverage within two or three hours after finishing a shift without a marked reaction. These reactions included substernal pressure, precordial "palpitation," fullness in the head and severe, acute illness. There were 17 non-drinkers in the group. An additional 83 workers were aware of no change in their tolerance for, or reaction to, alcohol.

#### COMMENT

With a given exposure to dinitrotoluene one cannot predict, on the basis of a pre-employment medical examination, which apparently healthy workman will show an unfavorable reaction and which workman will probably get neither symptoms or signs of intoxication. Our experience indicates a remarkable variation in the susceptibility of workmen to their environment. The workman who tolerates dinitrotoluene exposure for the first two weeks is more apt than not to tolerate that exposure indefinitely.

In their psychological reactions the subjects of this study show two outstanding attitudes. One attitude is that their work is the object of careful, continuous supervision by safety engineers, that their health receives particular attention from the physicians and, hence, they have one of the best jobs at their plant. With this attitude the workers belittle and dismiss minor and incidental complaints. The other equally significant attitude is one arising from an anxiety neurosis. The latter group of men unquestionably overemphasize their complaints and by introspection

apply to themselves symptoms which they have heard fellow workmen describe. The latter group undoubtedly influence to some extent the incidence of complaints in this report. The objective physical findings and laboratory reports, on the other hand, must be accepted at face value.

Through the insistence upon the application of acceptable personal hygiene (washing of hands, face and head before meals, careful showering after each shift, cleanliness of lockers, clothes and underwear) and the application of useful engineering and operating principles, we have observed a steady monthly decrease in evidence of dinitrotoluene intoxication. Prevention of complaints is entirely possible where intelligent cooperation of the individual workman is obtained. He must learn his new job in the war effort. In older plants where only experienced workers handle dinitrotoluene, symptoms or signs of intoxication were unheard of last year.

## SUMMARY

An increase in the signs and symptoms of chemical intoxication has appeared following the introduction of a large number of inexperienced workmen into manufacturing operations using dinitrotoluene.

The chief symptoms of a group of 154 workers so exposed were an unpleasant metallic taste, weakness, headache, loss of appetite, and dizziness. Two-thirds of the men in the group selected for study had these complaints at one time or another during the past twelve months. One-half the group developed objective signs of intoxication. These signs were chiefly pallor, cyanosis and low-grade anemia. Jaundice was seen but twice. No instances of permanent physical impairment were found.

Careful, frequent examinations of workmen in dinitrotoluene appear to be essential in proper supervision of particular operations.

## REFERENCES

1. Friedlander, A.: Clinical Observations of Intoxications with Benzene and Toluene Derivatives, with Special Consideration of the So-called Anilismia. *Neurologisches Centralblatt*, 19:155-162 and 294-297, 1900.
2. Koelsch, F.: Contributions to the Toxicity of Aromatic Nitro Compounds. *Zentr. Gewerbehyg. Unfallverhüt.*, 5:60, 65, 98, 109, 142, 1917.
3. Perkins, R. G.: A Study of the Munitions Intoxications in France. U. S. Public Health Reports, 34:2335-2374, Oct., 1919.
4. Courtois-Suffit: Toxicology of Dinitrotoluene and Pathology of the Workmen Handling It. *Arch. des Maladies Professionnelles*, 1:254-7, 1938.
5. Legge, T. M.: Industrial Poisoning in Chemical Manufacture. Review of War Years. *Chemical Trade J.*, 65:385-8, 411-3, 1919.
6. Hamilton, Alice: Hygienic Control of the Aniline Industry in Europe. *Textile Colorist*, 42:325-328, 399-400, 402, 471-472, 475, 1920.
7. von Oettingen, W. F.: The Aromatic Amino and Nitro Compounds, Their Toxicity and Potential Dangers; a Review of the Literature. Public Health Bulletin No. 271, U. S. Public Health Service, Washington.
8. Schwartz, Louis: Skin Hazards in Manufacture of Explosives. Public Health Bulletin No. 249, p. 82, 1939, U. S. Public Health Service, Washington.

## The Efficacy of the Drip Method in the Reduction of Gastric Acidity\*

By

ALBERT CORNELL, M.D., FRANKLIN HOLLANDER, Ph.D.

and

ASHER WINKELSTEIN, M.D.

NEW YORK, NEW YORK

THE two major advances in the medical therapy of peptic ulcer in recent years have been: (a) the continuous intragastric milk drip for controlling excessive gastric acidity, introduced by Winkelstein (1, 2) in 1931, and employing the excellent buffer qualities of milk; and (b) the use of colloidal non-absorbable antacids, as exemplified by aluminum hydroxide and aluminum phosphate gels.

Twenty-five years ago, Cloetta (3) described an astringent non-absorbable aluminum hydroxide powder for use in diarrhea. At the French Congress of Medicine in 1922, Roch (4) of Geneva called attention to the use of this preparation as an antacid because of its excellent acidity-reducing qualities. Its use in the United States was first reported in 1925 by Kagan (5) and by Crohn (6) in 1929, both of whom obtained favorable results with it. However, it remained for Einsel and Rowland (7) in 1932 to discover that, in spite of its clinical efficacy, the dried powder had practically no acidity-reducing action, as shown by

the direct titration with N 10 HCl. They therefore prepared a hydrous alumina gel which could take up at least ten times its own volume of N 10 acid, apparently by reason of its colloidal state and hence its increased adsorbent properties. Woldman and Rowland (8) found that a 7 per cent colloidal suspension of aluminum hydroxide may take up twenty to twenty-five times its own volume of N 10 HCl in forty minutes.

Winkelstein had previously demonstrated the occurrence of a high nocturnal acidity in ulcer patients (9), and to control this he used a milk-NaHCO<sub>3</sub> mixture in his continuous intra-gastric drip procedure. Using this same technique, Woldman and Rowland substituted a dilute aluminum hydroxide gel for the milk and obtained an efficient neutralization. Clinically, reports on the use of colloidal aluminum hydroxide preparations both by oral and by drip administration have been favorable [Einsel, Adams and Meyers (10), Emery and Rutherford (11), Eads (12), Levin and Shushan (13), Jones (14), Connelly (15), and others (16, 17, 18, 19, 20, 21, 22).] Because of the excellent clinical value of the drip method of treating peptic ulcer, it seemed desirable to us to compare the neutralizing effects of certain of these colloidal alumi-

\*This work was supported in part by a grant from John Wyeth and Brother.

From the Laboratories and the Gastro-Intestinal Clinic, The Mount Sinai Hospital, New York City.

†The aluminum preparations used in this investigation were the hydroxide (Amphojel) and the phosphate, both of which were kindly supplied to us by John Wyeth and Brother, Inc.

Submitted March 5, 1942.

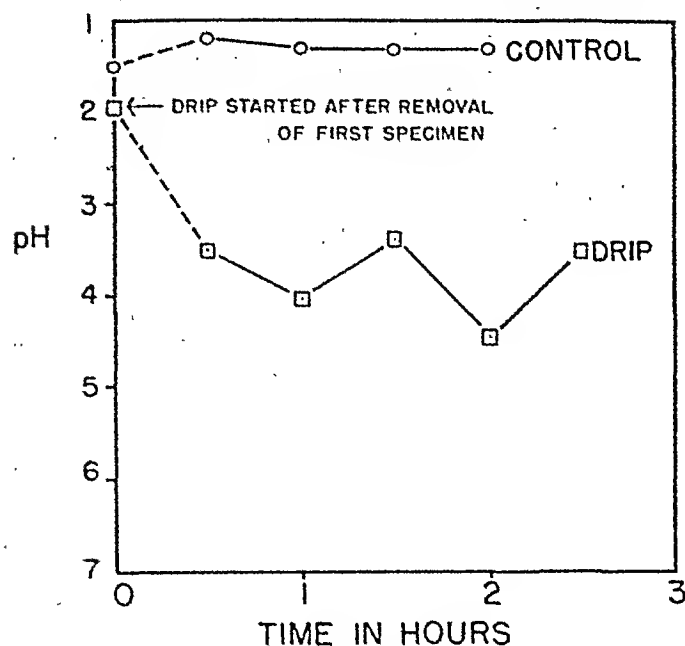


Fig. 1. Illustrative pH-curve for a fractional analysis during continuous drip treatment with milk- $\text{NaHCO}_3$  (Series A.) Patient: S. D.—ambulatory duodenal ulcer. Samples collected from 9:30 a.m. to 12:00 a.m. (Note: the pH-value corresponding to zero time on the "drip" graph should be 1.6 instead of 2.0.)

num preparations† with milk to which a soluble alkali had been added. The present contribution is a report of such an investigation, and is concerned with both day and night secretion, and with ambulatory and hospitalized patients.

#### PROCEDURE

Four series of experiments were carried out as follows:

**Series A**—The first group involved ambulatory peptic ulcer patients (1 gastric and 10 duodenal) without symptoms of pyloric obstruction. A control acidity curve was first obtained as follows: the fasting patient took a standard breakfast consisting of 2 tablespoonfuls of cooked farina with half a cup of milk and one teaspoonful of sugar, one glass of milk and one slice of soft white bread with sweet butter. One hour later, the stomach was aspirated completely, after which a sample was taken every thirty minutes for three hours. In this way a curve of secretion following a standard Sippy meal was obtained. On the following visit to the clinic, a few days later, the patient ate a similar breakfast, but immediately after the first aspiration, a continuous drip of milk and  $\text{NaHCO}_3$  at room temperature was administered at a rate of about 150 cc./hour. Aspirations were then made every thirty minutes, the stomach being completely emptied each time and the volume noted. The contents were well mixed and after removing a sample for study the remainder was returned to the stomach. This method of sampling was employed in all experiments. No medication was permitted for 12 hours preceding the experiment. The milk drip with one level teaspoonful of sodium bicarbonate to the quart was run by the gravity method at a rate of 20-30 drops per minute. On a third visit, the foregoing was repeated, except for the replacement of milk by the aluminum hydroxide gel diluted with 3 volumes of

water, this mixture being run at the rate of 15-20 drops per minute (about 150 cc./hour) by a special drip apparatus (see Cornell and Hollander, 1941 (23.)) In most of this group, a fourth visit permitted an additional study using aluminum hydroxide diluted with 4 volumes of milk without  $\text{NaHCO}_3$  (at a rate of about 120 cc./hour.)

**Series B**—Another group of these clinic patients (1 gastric, 12 duodenal, 1 jejunal ulcer) was studied similarly in order to compare the efficacies of aluminum hydroxide and aluminum phosphate drips. The latter being thinner than the hydroxide, it was employed without dilution but at the same rate: viz. 15-20 drops per minute (about 120 cc./hour as compared with 100 cc./hour for the diluted hydroxide in this series.)

**Series C**—Hospitalized patients with peptic ulcer (1 gastric, 7 duodenal, and 1 with both) were studied on the wards. These patients were of a refractory type, who had failed to respond satisfactorily to ambulatory therapy. No medication was given on the day preceding each test. Supper was served at 5 p.m.; 2 hours later (7 p.m.) gastric aspirations were started and repeated every 2 hours (9 and 11 p.m., 1, 3, 5 and 7 a.m.) for a total period of 12 hours. In this way, an acidity curve was obtained for the interdigestive phase of secretion. The milk- $\text{NaHCO}_3$  and aluminum hydroxide continuous drips were administered on successive nights (the rates averaged around 100 and 42 cc./hour respectively.) The stomach was aspirated completely every two hours, the total volume was noted, a sample was removed for analysis after mixing, and the remainder returned to the stomach.

**Series D**—A special group of ward cases (4 duodenal ulcers) with pyloric obstruction was studied in a similar way.

#### EXAMINATION OF THE GASTRIC SPECIMEN

The specimens were examined grossly for the presence of bile, food and mucus. They were then

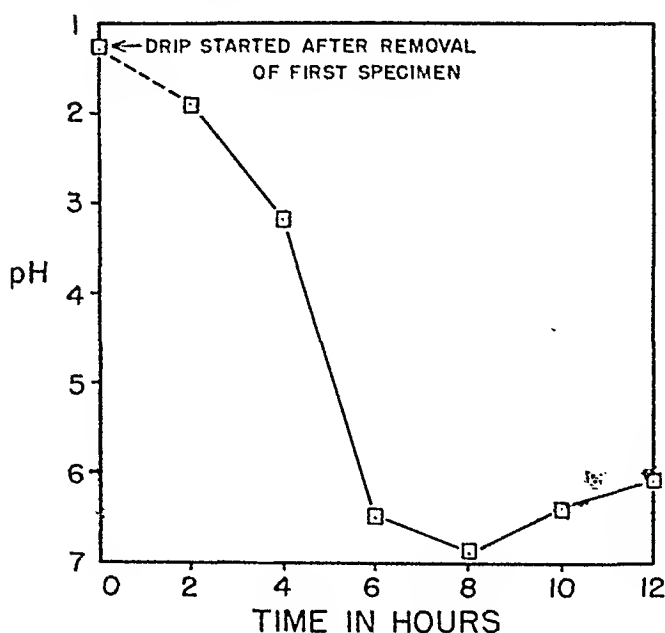


Fig. 2. Illustrative pH-curve for a fractional analysis during continuous drip treatment with milk- $\text{NaHCO}_3$  (Series C.) Patient: J. W.—hospitalized duodenal ulcer. Samples collected from 7 p.m. to 7 a.m.



filtered and the acidity (pH) determined by means of the glass electrode, although no appreciable difference in the pH value was noted as a result of filtration. All the specimens were studied electrometrically because the presence of considerable amounts of buffer substances in milk and in the aluminum preparations precluded the use of ordinary titrimetric methods on gastric samples which contain these substances. In the presence of considerable amounts of buffer mixtures, titration by means of burette and indicator is rarely reliable quantitatively, for the following reasons: (a) the end-point lacks sharpness because the titration curve possesses a gradual slope instead of a sharp point of inflection, (b) many indicators are changed in color and pH characteristics by the colloidal absorbents present in such gastric specimens. However, specimens collected for studies of fasting night secretion on nights when the drip therapy was not used could be examined titrimetrically for free and total acidities as well as electrometrically for pH. Such titrations were done by the semi-micro method described by Hollander (24), in which phenol red and bromphenol blue are the indicators, and pH-values of 3.5 and 7.0 are the end-points for free and total acidity respectively. When pH-values were calculated from such titration data for free acidity, we found

that estimated values were in reasonably good agreement with the pH-values determined directly on the same specimens by the glass electrode.

## RESULTS

### Milk-NaHCO<sub>3</sub>

Fig. 1 contains an illustrative pH-curve for a control fractional analysis in an ambulatory duodenal ulcer patient. The initial pH (fasting contents) was 1.5 (corresponding to a titrimetric free acidity of about 36 mN.) A maximum acidity (minimum pH of 1.2, corresponding to about 70 mN.) was reached in half an hour, after which the acidity fell to a pH of 1.3 and stayed there throughout the series. On the other hand, the second graph, which corresponds to the administration of milk-NaHCO<sub>3</sub>, shows a precipitate fall in acidity from a fasting level of pH 1.6 to 3.5, and remains between 3.4 and 4.4 throughout the period of treatment. In 58 specimens from the control analyses on all 11 cases of this series, the mean pH was 1.5 (see Table I), whereas the mean pH during milk drip treatment was 4.0 (for 61 specimens.)† The corresponding pH ranges for these groups are 1.1-3.3 for control specimens and 1.5-8.8

†The first ("fasting") specimen was excluded in all these and subsequent calculations. Mean pH-values were calculated as such, without regard to the logarithmic nature of the pH concept.

TABLE I  
Statistical summary of the data obtained in all four series

| Series  | Type of Case   | Number of Cases | Data*    | Results with Each Type of Drip Treatment |                         |                 |                      |                 |
|---------|--|-----------------|----------|--|-------------------------|-----------------|----------------------|-----------------|
|         |  |                 |          | Control                                  | Milk-NaHCO <sub>3</sub> | Alumin. Hydrox. | Milk-Alumin. Hydrox. | Alumin. Phosph. |
| (1)     | (2)  | (3)             |          | (4)                                      | (5)                     | (6)             | (7)                  | (8)             |
| A       | Ambulatory cases (clinic.) Drip continued for 3 hours. Samples taken every ½ hour.                         | 11              | Mean pH  | 1.5                                      | 4.0                     | 3.8             | 3.8                  |                 |
|         |  |                 | S.E. (±) | 0.05                                     | 0.26                    | 0.19            | 0.28                 |                 |
|         |  |                 | pH range | 1.1-3.3                                  | 1.5-8.8                 | 1.1-7.8         | 1.4-7.4              |                 |
|         |  |                 | N        | 58                                       | 61                      | 44              | 41                   |                 |
| B       | Ambulatory cases (clinic.) Drip continued for 3 hours. Samples taken every ½ hour.                         | 14              | Mean pH  | 1.7                                      |                         | 3.3             |                      | 4.0             |
|         |  |                 | S.E. (±) | 0.07                                     |                         | 0.14            |                      | 0.16            |
|         |  |                 | pH range | 1.2-4.2                                  |                         | 1.1-7.4         |                      | 1.5-8.3         |
|         |  |                 | N        | 68                                       |                         | 64              |                      | 69              |
| C       | Hospitalized cases (ward.) Drip continued all night. Samples taken every 2 hours.                          | 9               | Mean pH  | 1.4                                      | 4.0                     | 3.3             |                      |                 |
|         |  |                 | S.E. (±) | 0.04                                     | 0.26                    | 0.24            |                      |                 |
|         |  |                 | pH range | 1.1-2.0                                  | 1.2-8.0                 | 1.1-6.0         |                      |                 |
|         |  |                 | N        | 40                                       | 63                      | 48              |                      |                 |
| D       | Hospitalized cases with pyloric obstruction (ward.) Drip continued all night. Samples taken every 2 hours. | 4               | Mean pH  | 2.5                                      | 2.8                     | 3.2             |                      |                 |
|         |  |                 | S.E. (±) | 0.43                                     | 0.30                    | 0.25            |                      |                 |
|         |  |                 | pH range | 1.2-8.0                                  | 1.3-6.5                 | 1.3-7.7         |                      |                 |
|         |  |                 | N        | 22                                       | 24                      | 23              |                      |                 |
| A, B, C | All combined, excluding those with pyloric obstruction.  | 34              | Mean pH  | 1.5                                      | 4.0                     | 3.5             | 3.8                  | 4.0             |
|         |  |                 | S.E. (±) | 0.04                                     | 0.18                    | 0.11            | 0.28                 | 0.16            |
|         |  |                 | pH range | 1.1-4.2                                  | 1.2-8.8                 | 1.1-8.0         | 1.4-7.4              | 1.5-9.3         |
|         |  |                 | N        | 166                                      | 124                     | 156             | 41                   | 69              |

\*Definition of terms in "Data" Column:

Mean pH—the arithmetical mean of the pH values (disregarding their logarithmic nature) of all specimens except the first of each test (fasting contents.)

S.E.—the standard error (standard deviation of the mean.)

pH range—the maximum and minimum pH values observed.

N—the total number of specimens collected, irrespective of the individual patient.

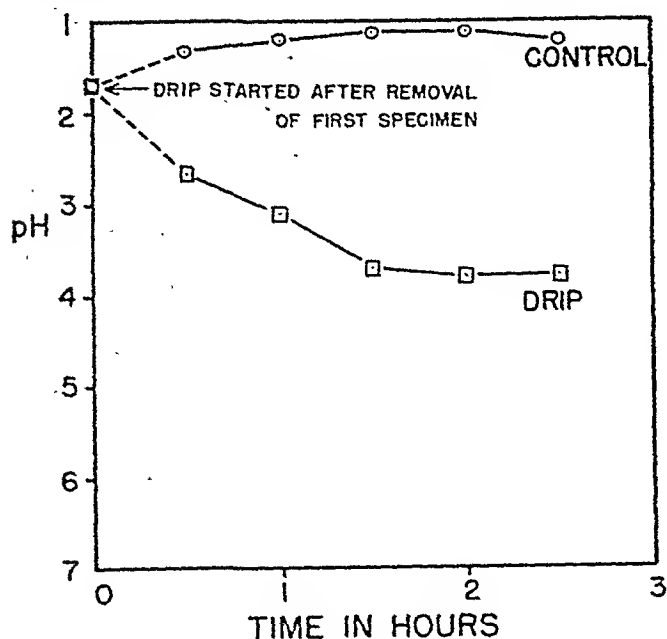


Fig. 3. Illustrative pH-curve for a fractional analysis during continuous drip treatment with aluminum hydroxide (Series A.) Patient: P. K.—ambulatory duodenal ulcer. Samples collected from 9:30 a.m. to 12:00 a.m.

for those under treatment. It is interesting to note that these control values correspond to the observations of Norgaard (25) who also found a mean pH of 1.5 in a series of patients with gastric ulcer.

For the hospitalized ulcer cases (Series C), the average results of our observations on the night secretion following an evening meal were identical with the foregoing for ambulatory cases. Thus, the control post-prandial analyses yielded a mean pH of 1.4, whereas for the milk drip treatment following the evening meal, the mean pH was 4.0.

However, the ranges of variation for this series are somewhat different from those for the ambulatory patients, being 1.1-2.0 for controls and 1.2-8.0 for milk drip pH's. This difference is well illustrated by Fig. 2, wherein the milk drip pH-values for specimens taken two or more hours after treatment was started fluctuate between 1.9 and 6.9.

The hospitalized cases with pyloric obstruction (Series D) are less satisfactory in this regard. For the control analyses, the mean pH is 2.5 (corresponding to a titrimetric free acidity of about 25 mN) which is considerably higher (i.e., lower acidity) than for the unobstructed cases. But during milk-drip therapy the pH rises only to 2.8 which differs from the control value by an amount that is statistically insignificant. These results clearly indicate the virtual failure of milk-drip therapy in affecting an adequate control of gastric acidity in cases of pyloric obstruction.

It follows that in the ulcer cases without obstruction, the milk  $\text{NaHCO}_3$  drip was able to elevate the pH to a mean value of 4.0. Now, Michaelis (26) considers most of the free HCl as being neutralized at a pH of 3.0, (close to the end-point of Topfer's reagent), whereas Hollander (24) adopted 3.5 as the titrimetric end-point for free acidity because this pH corresponds to an HCl concentration of 1 mN. Kirsner and Palmer (27) arbitrarily consider a pH of 4.0-5.0 as indicative of the effective control of gastric acidity,

but they state that it is possible that the healing of ulcers may occur at a lower pH. As recently pointed out by Hollander (28), an antacid must raise the pH to about 4.5 to effect practically complete elimination of peptic activity, but any gastric pH-value higher than this will be no more efficient so far as the desired end is concerned. However, at a pH of 3.5 acid irritation is completely eliminated, even though the proteolytic neutralization point has not quite been reached and about ten per cent of the peptic activity may still persist. For purposes of comparison, it should be noted that a change in pH from 1 to 3.5 represents a reduction in titrimetric acidity from 120 mN to about 1 mN. Since in our studies the pH was raised to 4.0 (both in the ambulatory 3-hour drip cases and in the hospitalized 12-hour night drip cases) it may be concluded that, under our conditions of treatment and observation, the milk- $\text{NaHCO}_3$  drip succeeded in maintaining, on the average, a degree of titrimetric acidity well below (pH well above) that which corresponds to "no free acid."

#### ALUMINUM HYDROXIDE

Analysis of the data obtained with aluminum hydroxide drip yielded very similar results. For all the ambulatory cases (Series A and B combined), the mean control pH (126 specimens) is 1.6 whereas in the aluminum hydroxide drip series it is 3.5 (108 specimens.) The graphs of Fig. 3 illustrate this difference very clearly; the control pH-values vary between 1.7 and 1.1, but during drip treatment they range from 2.7 to a maximum of 3.8. The results with the mixture of aluminum hydroxide and milk were almost identical with the foregoing, since the mean for 41 specimens on these same patients (Series A only) is also 3.8 pH-units.

For the hospitalized cases under treatment with the aluminum hydroxide drip during the night (Series C) the results are essentially the same as the preceding. In the illustrative case of Fig. 4, the pH for the night secretion curve during drip treatment (i.e., for a

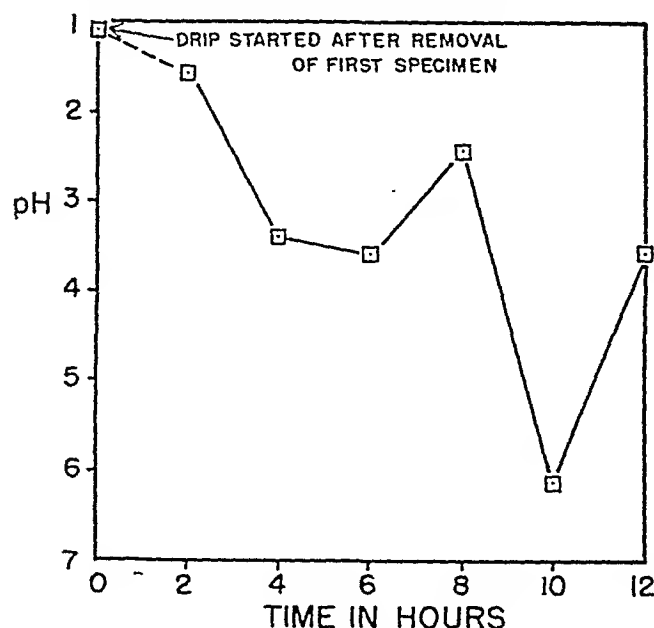


Fig. 4. Illustrative pH-curve for a fractional analysis during continuous drip treatment with aluminum hydroxide (Series C.) Patient: A. S.—hospitalized gastric ulcer. Samples collected from 7:00 p.m. to 7:00 a.m.

12 hour period of continuous night administration) ranges between 1.5 and 6.2. For all the 9 cases studied in this way, the pH-ranges are 1.1-2.0 (with a mean of 1.4) for controls and 1.1-8.0 (with a mean of 3.3) for observations under treatment. Although both of these mean values are slightly higher than the analogous values for the ambulatory groups of Series A and B, the difference (0.2 pH-units) is statistically insignificant. Thus, the mean increase in pH as a result of night therapy ( $3.3-1.4 = 1.9$  units) is identical with that which resulted from day therapy of shorter duration ( $3.5-1.6 = 1.9$  units.) Concerning the hospitalized cases with pyloric obstruction (Series D), the mean pH for the aluminum hydroxide drip tests is 3.2, not significantly different from the corresponding value for the hospitalized cases without obstruction in Series C. However, for the control tests on the obstructed cases the mean is 2.5, as against 1.4 for the uncomplicated cases in Series C. Thus although the mean elevation in pH as a result of treatment is only 0.7 units—which is certainly not very great—the mean terminal acidity (pH 3.2) is comparable with that obtained in the other three groups.

From these data, therefore, it appears that, on the average and under our working conditions, the aluminum hydroxide drip succeeded in maintaining a pH-value close to that corresponding to "no free acid."

#### ALUMINUM PHOSPHATE

There remains to be discussed the single group of ambulatory ulcer patients which were treated with the phosphate drip (Series B.) For 69 specimens obtained in such tests, the mean pH is 4.0—as high as any obtained with either milk- $\text{NaHCO}_3$  or aluminum hydroxide. This mean is 0.7 units greater than the mean obtained with the hydroxide drip in the same patients, and since the standard error of this difference is 2.1, it may be concluded that the difference is

statistically significant (significance ratio = 3.3.) From this it may be inferred that the aluminum phosphate drip was more effective in reducing the gastric acidity than was the hydroxide, but this may have resulted from the fact that the phosphate was used undiluted and therefore that the patient received a greater quantity of the phosphate per unit time than he did of the aluminum hydroxide.

#### FREQUENCY DISTRIBUTIONS FOR ALL OBSERVATIONS

The foregoing discussion of our data is presented in terms of mean pH-value and range of variation for each group of tests. These are the usual methods for the statistical analysis of data such as ours, and when combined with evaluations of standard error they constitute adequate measures of group variations for work of this kind. However, granting that any particular antacid therapy yields a mean pH which is well above that corresponding to "no free acid," there still remains the important question: What proportion of all the specimens in any one group of tests actually possess no free acid, only minimal concentrations of free acid (say 10 mN, which corresponds to a pH value of 2.0), or concentrations of considerable magnitude in spite of the drip treatment? In order to answer this question we have performed a frequency analysis of the individual pH-data grouped by series and test.

A summary of the results is presented in Table II, wherein the data are broken down into 3 classes, according to pH range: (1) pH 1.0-2.0, corresponding to a free acidity greater than 10 mN; (2) pH 2.0-3.5, corresponding to a very low degree of free acidity (1-10 mN), and (3) pH 3.5 and above, corresponding to no free acid (less than 1 mN.) By comparing the percentage of specimens which fall within each of these three ranges, it is possible to acquire even more

TABLE II  
*Frequency distribution of individual pH-values (all data)*

| Series | Type of Case                   | Type of Treatment      | Number (and Per Cent) of Specimens in Each Acidity Interval, Indicated in pH and Equivalent mN Concentration |  |                                    |           |
|--------|--------------------------------|------------------------|--|--|------------------------------------|-----------|
|        |                                |                        | High Free Acid<br>pH=1.0-2.0<br>mN=above 10  | Low Free Acid<br>pH=2.0-3.5<br>mN=10-1 | No Free Acid<br>pH=3.5-9.0<br>mN<1 | Total     |
| A      | Ambulatory cases               | Control                | 53 (91.4%)   | 5 (8.6%)                               | 0                                  | 58 (100%) |
|        |                                | Milk- $\text{NaHCO}_3$ | 14 (22.9%)   | 13 (21.3%)                             | 34 (55.8%)                         | 61 (100%) |
|        |                                | Alum. hydrox.          | 3 (6.8%)   | 10 (22.7%)                             | 31 (70.5%)                         | 44 (100%) |
|        |                                | Alum. hydrox.-milk     | 8 (19.5%)  | 14 (34.2%)                             | 19 (45.3%)                         | 41 (100%) |
| B      | Ambulatory cases               | Control                | 55 (80.9%)   | 11 (16.2%)                             | 2 (2.9%)                           | 68 (100%) |
|        |                                | Alum. hydrox.          | 10 (15.6%)   | 23 (35.9%)                             | 31 (48.5%)                         | 64 (100%) |
|        |                                | Alum. phos.            | 2 (2.9%)   | 26 (37.6%)                             | 41 (59.5%)                         | 69 (100%) |
| C      | Hospitalized cases             | Control                | 40 (100%)  | 0                                      | 0                                  | 40 (100%) |
|        |                                | Milk- $\text{NaHCO}_3$ | 19 (30.2%)   | 10 (15.9%)                             | 34 (53.9%)                         | 63 (100%) |
|        |                                | Alum. hydrox.          | 13 (27.1%)   | 14 (29.2%)                             | 21 (43.7%)                         | 48 (100%) |
| D      | Hospitalized cases, obstructed | Control                | 16 (72.7%)   | 3 (13.7%)                              | 3 (13.7%)                          | 22 (100%) |
|        |                                | Milk- $\text{NaHCO}_3$ | 7 (29.2%)  | 12 (50.0%)                             | 5 (20.8%)                          | 24 (100%) |
|        |                                | Alum. hydrox.          | 6 (20.7%)  | 11 (38.0%)                             | 12 (41.3%)                         | 29 (100%) |

information about the efficacy of any one drip procedure than is afforded by a simple comparison of average pH-values. Thus, from Series A we find that whereas none of the control specimens were entirely free of HCl and only 9 per cent fell in the low free acidity range, the milk- $\text{NaHCO}_3$  treated group yielded 56 per cent of acid-free specimens and 21 per cent of low free acid values. These numbers are quite as striking as the data of Table I in demonstrating the efficacy of the milk drip treatment; on the other hand they warn us that the milk drip does not eliminate the free acidity entirely, but only in 56 per cent of the specimens. The results with aluminum hydroxide-milk treatment in this series of ambulatory patients were very similar, but with the non-absorbable antacid alone they are distinctly better—71 per cent of the specimens being entirely acid-free and only 7 per cent in the high free acid group. Similar analyses of the data for the other series lead to essentially the same results, although treatment by milk and by aluminum hydroxide alone seem to be about on a par in Series C, the unobstructed hospitalized cases. The difference between the control groups of Series A and B—both ambulatory clinic patients—is indicative of the degree of experimental variation inherent in work of this kind. So far as the relative efficacies of aluminum phosphate and hydroxide (Series B) are concerned, the frequency distribution data are in accord with the difference between their mean values, discussed above.

#### DISCUSSION

It is widely recognized today that a major problem in ulcer therapy is the control of gastric acidity during the interdigestive phases, and particularly during the longest of these—the night phase. It is hardly necessary to emphasize the harmful effects which may arise from the presence of a highly active secretion in the ulcer-containing stomach, especially in the absence of food. All observers agree that the control of this type of secretion is fundamental in the medical management of the disease. The usual measures for this purpose—frequent feedings (Sippy diet), intermittent administration of absorbable and non-absorbable alkalis, atropine, *et al*—are all more or less successful with reference to day treatment, although frequent meals may in themselves serve to stimulate gastric secretion. During the night phase, however, these measures are essentially ineffective. It is illogical to treat an ulcer for part of the day and then to expose it to the strong corrosive action of an acid-pepsin mixture for the rest of the twenty-four hours, especially during the night when medication and feedings are ordinarily discontinued.

The specific measures which have been advocated in the past to meet this difficulty—gastric aspiration before retiring; large doses of atropine, alkalies, or olive oil; or periodic awakening of the patient for medication—have been found generally unsatisfactory. To meet this deficiency, the drip procedure was introduced by one of us (1) in 1931, using milk and  $\text{NaHCO}_3$ . Since that time, the use of the procedure has become widespread. In addition to the foregoing, the drip treatment possesses the following distinct advantages over intermittent procedures: (1) more effective control of night pain, (2) marked reduction in time of hospitalization required for healing of the ulcer, (3) the possibility of administering an adequate

diet with simultaneous continuous control of the interdigestive gastric secretion.

An objection to the milk- $\text{NaHCO}_3$  drip procedure may arise in patients who, for one reason or another, manifest a tendency to alkalosis; trouble also may be encountered in patients who are allergic to milk or possess some other idiosyncrasy. With the advent of colloidal aluminum preparations, the possibility of substituting such non-absorbable agents for the alkalized milk became manifest. Originally, hydrated aluminum hydroxide was the sole form in which these gels were prepared commercially. Subsequently, it was reported by Fauley, Ivy, Terry and Bradley (29) that dogs with experimental jejunal ulcers of the Mann-Williamson variety lost considerable amounts of phosphate in the feces when treated with aluminum hydroxide gels over long periods. To offset this difficulty, basic (hydrated) aluminum phosphate was introduced for antacid therapy and a gel of this substance is now available in quantity. In fact, we have found the phosphate preferable because its constipating effect is considerably less than that of the hydroxide preparation. Also, as a matter of clinical impression, the phosphate seems to have had a salutatory effect on the appetite of our patients, and this is in accordance with the views of Fauley and his coworkers.

It is generally recognized that these aluminum preparations are capable of neutralizing considerable quantities of dilute HCl in vitro and of elevating the pH to a value as high as 3.5. The effectiveness of their intragastric neutralizing action, however, particularly in patients with significantly high degrees of acidity, is another matter and one which has been awaiting adequate confirmation. In a comparative study of several antacid materials, Palmer and Kirsner (27) have actually questioned the efficiency of aluminum hydroxide as a neutralizing agent in the ordinary oral dosage of 1-2 teaspoonfuls every few hours. Hence we felt that it was desirable to investigate this question of neutralizing efficiency, especially in relation to the drip technique of ulcer therapy: since the milk- $\text{NaHCO}_3$  and aluminum hydroxide are in common use in this institution and since the phosphate gel offers several distinct advantages over the latter, we included all of these antacids in the present comparative study.

That all three preparations are considerably effective as intragastric neutralizing agents, even during prolonged night treatment, is amply demonstrated by our data. Under our conditions of treatment of 34 gastric and duodenal ulcer patients without obstruction, both the aluminum phosphate and the milk- $\text{NaHCO}_3$  maintained average pH's around 4.0; the aluminum hydroxide was somewhat less efficient, with a mean pH around 3.5—which is, nevertheless, the boundary value for "no free acid." Likewise, the percentages of individual samples with pH greater than 3.5 affords a good measure of the relative number of times when free acidity was completely absent or neutralized. For Series A, B and C, such a total reveals that in the control tests, free acid was absent in only about one per cent of the samples; with milk mixtures and aluminum hydroxide gel, this occurred in about 53 per cent and with aluminum phosphate in

about 60 per cent. Furthermore, if one chooses to be less rigorous in the specifications for reduction of acidity and is willing to accept pH 2.0 (10 mN) arbitrarily as a suitable criterion of adequate neutralization, then the milk drip was effective 75 per cent, the hydroxide 83 per cent and the phosphate 97 per cent of the time—in contradistinction to 11 per cent for the untreated control tests.

It must be pointed out that these data indicate that none of these drip therapy procedures succeeded in maintaining the stomach free of acid throughout the entire period of treatment. On the other hand, the proportion of high pH values, as well as the mean pH's, indicate considerable efficiency in acidity reduction. Furthermore, both these values may be materially increased by increasing the concentration of antacid in the drip fluid and by elevating the rate of flow above that employed throughout the treatment. In fact, the apparent antacid superiority of the phosphate gel over aluminum hydroxide and milk-NaHCO<sub>3</sub> may well be due to our use of the aluminum phosphate without dilution.

## SUMMARY

1. The control of gastric acidity by intermittent methods especially during the night is discussed and attention is called to the inadequacy of such procedures in general use for ulcer therapy.

2. Drip therapy affords a method for the continuous neutralization, throughout the twenty-four hour cycle.

3. A quantitative study of the relative merits and efficiencies of milk-NaHCO<sub>3</sub>, aluminum hydroxide gel, and aluminum phosphate gel, is reported in a group of 38 cases of peptic ulcer. All three are found to be extremely effective antacids when administered by continuous drip.

4. Neither the milk-NaHCO<sub>3</sub> nor the aluminum hydroxide gel was effective to any considerable degree in cases of pyloric obstruction.

The authors acknowledge their indebtedness to Drs. George Bachr and Bernard S. Oppenheimer for the use of clinical material on their respective medical services in this hospital.

## REFERENCES

- Winkelstein, A.: Studies in Gastric Secretion During the Night with a Preliminary Note on a New Therapy for Peptic Ulcer. *Am. J. Surg.*, 15:523, 1932.
- Winkelstein, A.: A New Therapy of Peptic Ulcer: Continuous Alkalinized Milk Drip Into the Stomach. *Am. J. Med. Sci.*, 135:695, 1933.
- Cloetta, M.: Ein Neues Mittel zur Bekämpfung des Dorchfalls. *Corresp. f. Schweiz. Aerzte*, 30:247, 1916.
- Roch, M.: *Compt. Rend. Congres Francoise de med.*, Paris, p. 101, 1922. (Quoted by Kagan.)
- Kagan, S. R.: The Treatment of Gastric Ulcer and Hyperchlorhydria. *Clin. Med.*, 32:229, 1925.
- Crohn, B. B.: The Clinical Use of Colloidal Aluminum Hydroxide as a Gastric Antacid. *J. Lab. Clin. Med.*, 14:519, 1929.
- Einsel, I. H. and Rowland, V. C.: The Aluminum Hydroxide Treatment of Peptic Ulcer. *Ohio State Med. J.*, 28:173, 1932.
- Woldman, E. E. and Rowland, V. C.: Continuous Acid Adsorption by Aluminum Hydroxide Drip in the Treatment of Peptic Ulcer. *Rec. Gastroent.*, 3:27, 1936.
- Winkelstein, A.: One Hundred and Sixty-Nine Studies in Gastric Secretion During the Night. *Am. J. Dig. Dis. and Nutrit.*, 1:778, 1935.
- Einsel, I. H., Adams, W. L. and Myers, V. C.: Aluminum Hydroxide in the Treatment of Peptic Ulcer. *Am. J. Dig. Dis.*, 1:513, 1934.
- Erdery, E. S., Jr. and Rutherford, R. B.: Studies on the Use of Aluminum Hydroxide Gel in the Treatment of Peptic Ulcer. *Am. J. Dig. Dis.*, 5:486, 1938.
- Eads, J. T.: Clinical Results from the Continuous Intragastric Drip Using Colloidal Aluminum Hydroxide in the Treatment of Peptic Ulcer. *Am. J. Dig. Dis.*, 7:32, 1940.
- Levin, A. L. and Shushan, M.: Recent Progress in the Diagnosis and Treatment of Gastric and Duodenal Ulcer. *New Orleans Med. and Surg. J.*, 91:120, 1935.
- Jones, C. R., Jr.: Colloidal Aluminum Hydroxide in the Treatment of Peptic Ulcer. *Am. J. Dig. Dis. and Nutrit.*, 4:99, 1937.
- Connelly, R. C.: Colloidal Aluminum Hydroxide Therapy in Upper Gastro-Intestinal Lesions. *J. Mich. State Med. Soc.*, 37:406, 1938.
- Swain, W. A.: Aluminum Silicate (Kaolin) with Aluminum Hydroxide in Certain Intestinal Disorders. *Med. Rec.*, 140:26, 1934, 68, 1934.
- Kyger, E. R., Jr., Hashinger, E. H. and Wilhelmj, E. W.: The Treatment of Peptic Ulcer with Colloidal Aluminum Hydroxide. *Am. J. Dig. Dis.*, 6:363, 1939.
- O'Brien, M. M.: Treatment of Peptic Ulcer by Continuous Drip Method. *Med. J. Australia*, 2:559, 1938.
- Kunstler, M. B.: The Treatment of Inflammation of Stomach with Colloidal Cream of Aluminum Hydroxide Lavage. *Med. Rec.*, 149:268, 1939.
- Bennett, T. I. and Gill, A. M.: Colloidal Aluminum Hydroxide in the Treatment of Peptic Ulcer. *Lancet*, 1:500, 1939.
- Steigmann, F.: Colloidal Aluminum Hydroxide Continuous Drip in Treatment of Large Gastric Ulcer. *Illinois Med. J.*, 76:143, 1939.
- Woldman, E. E. and Polan, C. G.: Value of Colloidal Aluminum Hydroxide in the Treatment of Peptic Ulcer—407 Consecutive Cases. *Am. J. Med. Sci.*, 193:155, 1939.
- Cornell, A. and Hollander, F.: An Improved Continuous Drip Apparatus, etc. *Rec. Gastro-Enterol.*, 9, In press 1942.
- Hollander, F.: Studies in Gastric Secretion. II. A Comparison of Criteria of Acidity, etc. *J. Biol. Chem.*, 91:451, 1931.
- Norraard, A.: Colorimetric pH Determinations of Test Meal Filtrates in Patients with Gastric Diseases. *Acta Med. Scand.*, 60:438, 1924.
- Michaelis, L.: Some Problems Concerning the Gastric Juice. *Harvey Lectures*, Series 22, 1926-7.
- Kirsner, J. B. and Palmer, W. L.: Effect of Various Antacids on the H-Ion Concentration of the Gastric Contents. *Am. J. Dig. Dis.*, 7:85, 1940.
- Hollander, F.: What Constitutes Effective Neutralization of Gastric Contents? *Am. J. Dig. Dis.*, 6:127, 1939.
- Fauler, G. B., Ivy, A. C., Terry, L. and Bradley, W. B.: An Attempt to Prevent Post-Operative Jejunal Ulcer by Aluminum Hydroxide Therapy. *Am. J. Dig. Dis.*, 5:792, 1939.

## Chronic Gastric Ulcer in a Six Year Old Child\*

By

MANFRED KRAEMER, M.D.†

NEWARK, NEW JERSEY  
and

LESLIE TOWNSEND, M.D.‡

ROSELLE, NEW JERSEY

IT is difficult to accurately determine from the literature the number of cases of chronic gastric ulcer in children that have been reported. This difficulty presents itself for three reasons: First, cases of peptic ulcer in children are often reported with cases

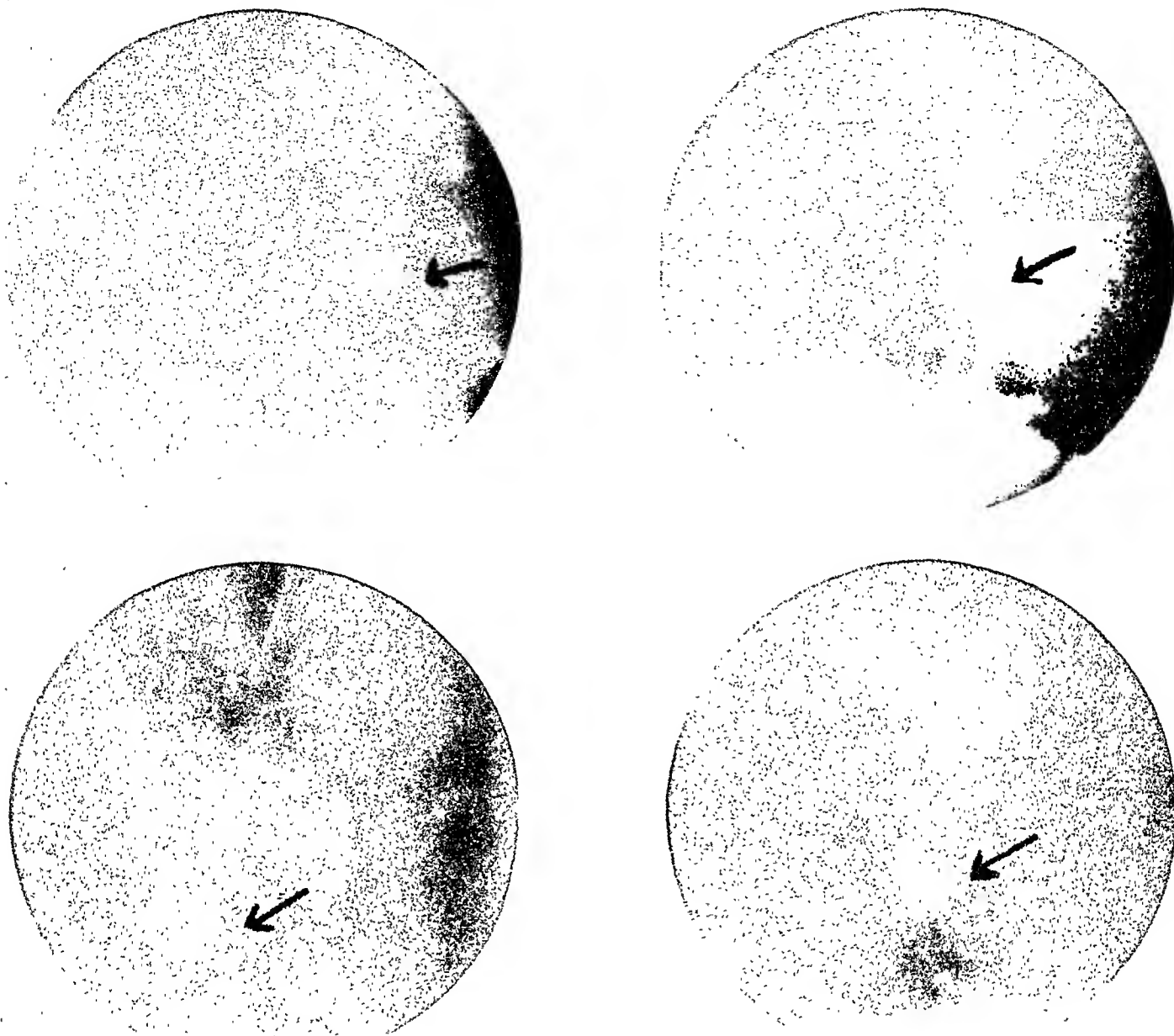
of peptic ulcer in the newborn. Ulcerations of the stomach and duodenum frequently resulting in death from hemorrhage or perforation are common immediately after birth, and in the first year of life. This type of acute ulceration should not be confused with chronic peptic ulcer. Second, because cases are reported under the term chronic peptic ulcer, and include both gastric and duodenal ulcer. Third, because

\*From the Presbyterian Hospital in Newark, New Jersey.

†Visiting physician.

‡Associate, Gastro-Intestinal Clinic.

Submitted March 21, 1942.



Spot films of ulcer at various angles.

authors estimates of the end of childhood vary from the age of twelve to fifteen.

Proctor (1), in a review of the literature in 1925 listed 11 cases of gastric ulcer in children and added one case from the Mayo Clinic. Foshee (2) in 1932 added a case of his own and found six more cases in the literature making a total of 19. Logan and Walters (3) in May, 1941, reported 15 additional cases from the literature but three of these were under the age of two years (4 months, 5 months and 10 months.) This made a total of 34 cases and they added a second case from the Mayo Clinic making a total of 35 cases. Kellogg (4) in 1939 had reported a total of 21 cases of gastric ulcer in children but gave no criteria for his choice.

In the most comprehensive review of the world literature on peptic ulcer in childhood published to date, Bird, Limper and Mayer (5) found a total of six cases of gastric ulcer reported between the ages of 2 and 6, and sixteen cases between the ages of 7 and 11,

or a total of twenty-two cases under twelve years of age.

Papers by Burdick (6) in 1940 and Moore (7) in 1941, were not included in the bibliography of Bird, Limper and Mayer. Burdick reported eight cases of peptic ulcer out of 21,231 admissions to the Children's Hospital of Washington, D. C., plus two private cases. Of the ten cases, two were gastric. One of the gastric ulcers was found post-mortem in a child of six, and the other was demonstrated on fluoroscopy in a child of ten. Moore reported eight cases of peptic ulcer from the records of the Vancouver General Hospital. Only one of these patients had a gastric ulcer. This, in a child of eleven, was diagnosed by radiography and fluoroscopy. These three cases should be added to those of Bird, Limper and Mayer, and make a total of 25 cases of gastric ulcer reported to date in children between the ages of two and eleven, and of seven cases between the ages of two and six.

We are reporting what is probably the eighth recorded case of gastric ulcer in children between the



ages of two and six, and the 26th case in children between the ages of two and twelve. Peptic ulcer in children must be much more common than is generally realized. Many ulcer bearing adults, if their memories are assisted by the physician, can trace their symptoms back to childhood. In most earlier reported cases, the diagnosis was made at autopsy after some such complication as melena, obstruction, or perforation, resulted in death. If X-ray studies were performed more freely on children with abdominal symptoms, more cases of peptic ulcer in childhood would doubtless be diagnosed. In the case here reported the crater could be seen only with the patient in the upright position, and only with a teaspoonful of barium mixture in the stomach.

### CASE REPORT

R. D. is an only child. An uncle has a duodenal ulcer. At the age of five the patient began to complain of left upper quadrant abdominal pain, lasting four or five minutes at a time. The pain seldom came more than once a day, usually before or during breakfast. It disappeared for intervals of a few weeks at a time, but had been present every morning during the week starting January 15, 1942. The patient vomited only once in the course of his illness, and then not in association with the pain. The appetite was good, and there were no other symptoms.

Physical examination showed no abdominal tenderness. The boy was bright and active. With the patient standing, after a teaspoonful of barium was swallowed, a niche could be seen on the posterior gastric wall in the body of the stomach. When the stomach was filled with barium, the niche could not be demonstrated. The duodenal bulb was normal.

The patient was placed on an ulcer regimen, and in five days the pains ceased. By February 2, 1942, occult blood was no longer present in the stools. On films taken February 16, no niche could be identified.

### SUMMARY

This is a report of a gastric ulcer in a six year-old child. The patient responded well to treatment.

### REFERENCES

1. Proctor, O. S.: Chronic Peptic Ulcer in Children. *S. G. O.*, 41:63, July, 1925.
2. Foshee, J. C.: Chronic Gastric Ulcer in Children: Report of a Case. *J. A. M. A.*, 99:1336, Oct. 15, 1932.
3. Logan, G. B. and Walters, W.: Chronic Gastric Ulcer in Childhood Treated Surgically. *Ann. Surg.*, 113:260, May, 1941.
4. Kellogg, H. B.: Chronic Peptic Ulcer in Children. *Northwest Med.*, 38:129, April, 1939.
5. Bird, C. E., Limper, M. A. and Mayer, J. M.: Surgery in Peptic Ulceration of Stomach and Duodenum in Infants and Children. *Ann. Surg.*, 114:526, Oct., 1941.
6. Burdick, W. F.: Peptic Ulcer in Children. Report of Ten Cases. *J. Pediatr.*, 17:554, Nov., 1940.
7. Moore, O. M.: Peptic Ulcer in Children. *Canadian Med. Ass'n J.*, 44:462, May, 1941.

## Anacidity and Gastritis Associated With Gastric Carcinoma

By

RUDOLF SCHINDLER, M.D.

and

WILLIAM M. SMITH, M.D.

CHICAGO, ILLINOIS

NUMEROUS theories have been advanced to explain the frequent occurrence of anacidity in gastric carcinoma. This paper will discuss especially the importance of chronic gastritis as cause of anacidity in gastric carcinoma. Bloomfield and Pollard (1) feel that the gastritis theory is best supported. This theory was probably developed first by Lebert (3) in 1878. Its first thorough discussion is due to Rosenheim, 1888 (5). He already differentiated three types of chronic gastritis. He found that one case of cancer with acid had a normal mucosa, but that in 14 cases with anacidity gastritic changes were present; atrophic patches were found at some distance from the tumor. Therefore, he believed the anacidity was entirely due to chronic gastritis. He thought that the differential diagnosis between chronic gastritis and gastric carcinoma by gastric analysis is impossible. Matthieu in 1889 (4) joined this view, which then became predominant, especially by Knud Faber's work (2).

The methods used to determine whether or not gastritis was present in our material were the gross, gastroscopic and the microscopic examination of the gastric mucosa. The gross gastroscopic inspection proved to be surprisingly reliable (6.) It must not be confused with the inspection of the bloodless specimen, in which only rarely is the diagnosis of a diffuse lesion of the gastric mucosa

possible. A comparison of the gastroscopic and microscopic aspect of the gastric mucosa will be published elsewhere. It may be summarized here by saying that in each case in which atrophic gastritis was found gastroscopically most definite atrophic gastritis was seen microscopically also. For this reason it seemed justifiable to include in our statistics 7 cases in which at gastroscopy most outspoken atrophy was seen, but in which no microscopic check had been possible. On the other hand, we found one case in which at gastroscopy a normal mucosa had been diagnosed but microscopically a rather severe atrophic gastritis was seen. Therefore, we decided not to include any case of gastroscopically normal mucosa without microscopic check.

It is not contended that cases described as presenting a normal mucosa are entirely devoid of inflammatory changes; the microscopic examination of every area in the gastric mucosa is practically impossible. For our purposes the gastric mucosa is considered to be normal if the mucosa appeared normal gastroscopically and if no abnormalities were seen histologically in the sections examined. Although there was almost complete agreement between both methods we are inclined to consider the gastroscopic method as the superior one, because a large surface of the mucosa is seen, whereas microscopically relatively small areas will be examined.

Our material consisted of 48 cases of gastric carcinoma in which sufficiently reliable studies of the gastric mucosa were possible. We believe that the range of the "normal" microscopic structure of the

pyloric antrum is not well known; only sections of the body mucosa, therefore, were used to establish its normal character. The gastric mucosa was considered to be *normal* gastroscopically if its color was uniform orange red and its surface was moist and glistening. It was considered to be normal histologically, if the surface epithelium consisted of uniform tall columnar mucus cells, if the pits had straight lumina, perpendicular to the surface, being lined by tall columnar mucus epithelium and occupying the upper fourth to fifth of the mucosal layer, the stroma between them containing only a moderate number of cells; if the gastric glands were closely packed, having between them only scant stroma with few cells; if only a few small lymphfollicles were seen.

*Chronic superficial gastritis* was diagnosed gastroscopically, if the color of the mucosa was "mottled"; if adherent secretion was present; if edema was seen. Microscopically this diagnosis was made if changes were found only in the stroma between the pits, this stroma being increased in amount, containing edema, numerous plasma cells, congested capillaries and small hemorrhages.

The diagnosis of *atrophic gastritis* was made gastroscopically, if patchy or diffuse graying and thinning with appearance of blood vessels was seen. Microscopically this diagnosis was made if the amount of glands was reduced: if there was cellular infiltration and edema between the rarified glands; if there were triangular cushions of connective tissue, resting on the split up muscularis mucosae; if there was proliferation of pits with metaplasia of the epithelium into an intestinal type with goblet cells and Paneth cells; and if the thickness of such a mucosa was reduced.

*Hypertrophic gastritis* was diagnosed gastroscopically, if the mucosa looked dull, swollen, velvety with formation of small nodules. Microscopically this diagnosis was made if the mucosa was thicker than normal (but without reduction of glands), this thickness being due either to dense lymphocytic infiltration between the glands with enlarged lymphfollicles, or to proliferation of the surface epithelium, or to proliferation of the glands themselves.

The results of this study are found on Table I.

*Normal mucosa:* In 10 cases the mucosa was found to be normal gastroscopically, and the most interesting result of our study is that in four out of ten cases no free HCl was present at the histamine test. This fact suggests that at least in some cases other factors than gastritis and anatomical degeneration of the mucosa might be responsible for the anacidity. The objection could be raised that at repeated histamine tests still some acid would have been found. However, transitory histamine-proved anacidity does not occur very often, and such a rare event can scarcely be expected to be present in four out of ten cases.

*Superficial gastritis:* There were 8 cases. We know that in some cases of superficial gastritis without carcinoma no free HCl is present (7.) These cases, however, are rather rare. The incidence of histamine-proved anacidity in our group (50%) is much higher than would be found in general statistics on chronic superficial gastritis. Therefore, it is not likely that the superficial gastritis is the cause or at least not the only cause of the histamine-proved anacidity in

our cases. Again it must be remembered that in superficial gastritis the glandular apparatus is intact.

*Atrophic gastritis:* 25 cases. Here the facts are more complicated. In nine cases free HCl was found, in 16 cases there was histamine-proved anacidity. It is true that in all cases of atrophic gastritis without carcinoma, approximately one-third have histamine-proved anacidity (8), but these statistics include all cases of mild patchy atrophic gastritis. In the carcinoma group the atrophy is usually severe and extensive. Therefore, it is entirely possible, though not proved that the atrophic gastritis is the sole cause of the anacidity found in 64% of this group.

Four cases of this group without acid are of special interest because case history and observations made it likely that histamine-proved anacidity existed before the development of the carcinoma and probably could be attributed to pre-existing gastritis.

In two of these cases (Unit No. 108909 and 200796) pernicious anemia was known to be present before the development of the carcinoma. Atrophic gastritis is found in practically all cases of pernicious anemia. Therefore, the conclusion must be drawn that in these cases atrophic gastritis with anacidity preceded the formation of carci-

TABLE I  
*Condition of the gastric mucosa compared with the secretion of acid in 48 cases of gastric carcinoma*

| Free HCl Present at Histamine Test |                        | No Free HCl Present at Histamine Test |
|------------------------------------|------------------------|---------------------------------------|
| 6                                  | Normal mucosa          | 4                                     |
| 4                                  | Superficial gastritis  | 4                                     |
| 9                                  | Atrophic gastritis     | 16                                    |
| 3                                  | Hypertrophic gastritis | 2                                     |
| 22                                 |                        | 26                                    |

noma. There was an idiopathic anemia present in the third patient (Unit No. 241004) also before she developed a carcinoma. This anemia had been treated successfully by combined liver-iron therapy; the exact differential diagnosis between pernicious and microcytic anemia was not possible by retrospective analysis. Atrophic gastritis is found in both diseases without exception and the patient had had histamine proved anacidity for many years. Therefore, the conclusion that atrophic gastritis plus anacidity preceded the carcinoma must be drawn for this case too. The fourth case has been described elsewhere (9), (Unit No. 188610.) Histamine proved anacidity with severe gastric distress preceded the very first appearance of a small nonulcerated carcinoma by 5 years. Together with this carcinoma a complete atrophy was found. It seems probable that the distress of the patient and the anacidity had been the result of severe atrophic gastritis.

*Hypertrophic gastritis:* 5 cases. Two of the five cases had histamine proved anacidity. Anacidity in hypertrophic gastritis has been described, but it is not frequent. However, two cases are not sufficient to permit any conclusion.

## CONCLUSIONS

1. In 48 cases of gastric carcinoma the uninvaded gastric mucosa was studied gastroscopically. In most cases a microscopic check of the gastroscopic findings became possible. An attempt was made to compare the findings with the secretion of acid.

2. Although chronic gastritis was found definitely in 38 cases, there were 4 cases in which a normal mucosa was found together with anacidity. These 4 cases indicate that chronic gastritis is not always the cause of anacidity in a stomach invaded by carcinoma.

REFERENCES

1. Bloomfield, A. L. and Pollard, H. S.: Gastric Anacidity: Its Relation to Disease. New York, Macmillan Company, 1935.  
2. Faber, K. and Lange: Die Pathogenese und Aetiologie d. chron. Achylia gastrica. *Ztschr. f. klin. Med.*, 66:53, 1896.

3. Lebert: Die Krankheiten d. Magens Tübingen, H. Laupp, 1878.  
4. Matthieu, Albert: Etat de la muqueuse de l'estomac dans le cancer de cet organe. *Arch. Gen. de Med.*, 163:402, 1889.  
5. Rosenheim, Th.: Über atrophische Prozesse an d. Magen-schleimhaut in ihrer Beziehung zum Carcinom, etc. *Berl. klin. Wchnschr.*, 25:1021, 1888.  
6. Schindler, R.: On Chronic Epigastric Distress and on the Anatomic Foundation of Chronic Gastritis. (Unpublished.)  
7. Schindler, R., Nutter, P., Groom, H. and Palmer, W. L.: Anatomic Foundation of Anacidity. *Arch. Int. Med.*, 66:1060, 1940.  
8. Schindler, R. and Murphy, H.: Symptomatology of Chronic Atrophic Gastritis. *Am. J. Dig. Dis.*, 7:7, 1940.  
9. Schindler, R. and Gold, R.: Gastroscoy in Gastric Carcinoma. *S. G. O.*, 69:1, 1939.

Diagnostic Value of Serum Cholinesterase Determinations in Jaundice and in Cirrhosis of the Liver

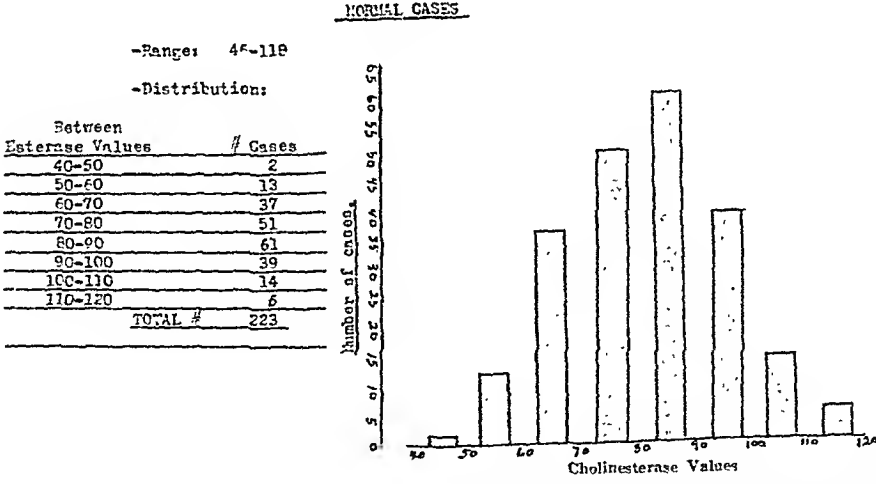
By

ARTHUR SCHIFRIN, M.D., LESTER TUCHMAN, M.D.  
NEW YORK, NEW YORK  
and  
WILLIAM ANTOPOL, M.D.  
NEWARK, NEW JERSEY

SINCE the discovery that an acetylcholine-like substance is responsible for all vagus activities in the body, interest in its physiological and pathological behavior has naturally been great. Due to its rapid destruction, direct measurement of acetylcholine in the blood is difficult, but the measurement of the amount of enzyme which causes its destruction can be determined with great accuracy since Ammon (1) in 1933 devised his gasometric method whereby one measures the amount of carbon dioxide liberated from a carbonate solution by the acetic acid formed from

McArdle (4) published his studies on cholinesterase in jaundice and diseases of the liver. He confirmed our findings of the occurrence of lowered values in liver disease and suggested that the determination of serum cholinesterase be used as an index of liver function. As his values were lower in non-obstructive jaundice of hepatic origin than in obstructive jaundice, he further suggested the use of this determination for the differential diagnosis of obstructive from non-obstructive jaundice.

In this paper a study of cholinesterase levels in 98



the hydrolysis of acetylcholine into its constituent parts. Since 1937 (2) we have been investigating acetylcholine esterase levels in serum in normals and in a host of varied clinical conditions. Among our earliest findings we noted that in certain types of jaundice and biliary tract disease cholinesterase levels were low. In 1938 (3) we reported a study of 28 such cases, the first in which this fact was found. This finding was empiric and has remained so. In 1940,

additional cases of hepatic and biliary tract disease will be presented; 75 with jaundice and 23 with cirrhosis of the liver without jaundice. Only those cases are included in this series in which the diagnosis was supported by necropsy, exploration, biopsy, or where these were not feasible—as in catarrhal jaundice, toxic hepatitis and often in cirrhosis—by strong clinical evidence. All cases not meeting rigorous criteria were excluded.

We found that maximum information could be obtained by dividing the cases into the following 8 groups:

From the Medical Services and the Laboratories of The Mount Sinai Hospital, New York City and The Division of Laboratories of The Newark Beth Israel Hospital, Newark, New Jersey.  
Submitted May 6, 1942.

TABLE I  
Serum Cholinesterase in Cases of Jaundice due to Common Duct Stone  
(without Complicating Cholangitis)

| Case Number | Sex | Age | Date  | Cholinesterase | Duration of Jaundice at Determination | Temperature | Hemoglobin % | Icteric Index (Acetone Method) | Cholesterol Ester Partition | Bile in Stools | Bile in Urine | Remarks   |
|-------------|-----|-----|-------|----------------|---------------------------------------|-------------|--------------|--------------------------------|-----------------------------|----------------|---------------|---|
| 1 M 31      | M   | 31  | 7/11  | 110            | 7 days                                | 99.6        | 105          | 15                             | 10                          | 0              | 1+            | Galactose Toler. 0.5 gm. Post-operative 11/15. Operation 7/14   |
| 2 F 65      | F   | 65  | 12/12 | 58             | 2 days                                | 91.6        | 43           | 25                             | 10                          | 0              | 1+            | Phosphatase 35. Operation 11/19.  |
| 3 F 25      | F   | 25  | 11/20 | 65             | 4 wks.                                | 99.2        | 43           | 25                             | 10                          | 0              | 1+            | Operation 11/19.  |
| 4 M 57      | M   | 57  | 11/27 | 51             | 1 wk.                                 | 99.6        | 70           | 25                             | 10                          | 0              | 1+            | Galactose 0.5 gm. Operation 12/14.  |
| 5 M 35      | M   | 35  | 7/6   | 70             | 5 days                                | 99.6        | 65           | 25                             | 10                          | 0              | 1+            | Galactose 0.5 gm. Operation 7/16.   |
| 6 F 29      | F   | 29  | 6/11  | 71             | 3 wks.                                | 99.6        | 70           | 25                             | 10                          | 0              | 1+            | Phosphatase 10. Operation 7/16.   |
| 7 M 36      | M   | 36  | 12/11 | 41             | 2 wks.                                | 99.6        | 100          | 25                             | 10                          | 0              | 1+            | Phosphatase 10. Operation 7/16.   |
| 8 F 41      | F   | 41  | 12/12 | 57             | 2 days                                | 99.6        | 27           | 12                             | 10                          | 0              | 1+            | Galactose 3.5 gm. Phosphatase 10.2. Operation 7/16. Ca. of pancreas.  |
| 9 F 23      | F   | 23  | 11/6  | 52             | 4 wks.                                | 99.6        | 84           | 25                             | 10                          | 0              | 1+            | Phosphatase 10. Operation 12/14.  |
| 10 M 62     | M   | 62  | 12/7  | 57             | 1 wk.                                 | 99.6        | 100          | 25                             | 10                          | 0              | 1+            | Phosphatase 10. Operation 12/14.  |
| 11 F 51     | F   | 51  | 1/3   | 60             | 4 days                                | 100.4       | 14           | 25                             | 10                          | 0              | 1+            | Operation 1/7.  |
| 12 M 55     | M   | 55  | 1/3   | 71             | 2 wks.                                | 99.6        | 21           | 25                             | 10                          | 0              | 1+            | Acute evidence of gall stones. Attacks of severe upper abdominal pain and jaundice.   |
| 13 F 59     | F   | 59  | 10/11 | 41             | 3 days                                | 100.2       | 10           | 7                              | 10                          | 0              | 1+            | Particular fibrillation. Hyperactive heart disease in failure. Severe abdominal pain. Jaundice and clay-colored stool lasting 5 days. Gall stones on x-ray. |
| 14 F 70     | F   | 70  | 1/24  | 57             | 5 days                                | 99.6        | 43           | 25                             | 10                          | 0              | 1+            | Gall stones on x-ray. Typical attacks of pain in right upper quadrant and back.   |
| 15 M 31     | M   | 31  | 1/4   | 62             | 1 wk.                                 | 99.6        | 70           | 25                             | 10                          | 0              | 1+            | Galactose 1 gm. Operation 1/7.  |
| 16 M 31     | M   | 31  | 1/4   | 60             | 1 wk.                                 | 99.6        | 70           | 25                             | 10                          | 0              | 1+            | Galactose 1 gm. Operation 1/7.  |
| 17 F 60     | F   | 60  | 7/7   | 54             | slight                                | 99.6        | 90           | 11                             | 10                          | 0              | 1+            | Operation 7/16.   |
| 18 F 40     | F   | 40  | 7/6   | 46             |                                       | 99.6        | 100          | 25                             | 10                          | 0              | 1+            | Operation 7/9.  |
| 19 F 47     | F   | 47  | 6/30  | 41             | 1 wk.                                 | 99.6        | 100          | 25                             | 10                          | 0              | 1+            | Galactose 3.5 gm. Operation 7/16.   |

\* Post-operative stool.  
+ Brown  
- Light  
0 - Clay

\*\* Icteric indices in this and following tables are all by the acetone method of Ernst and Forster, and are roughly 1/3 the values obtained by the water method.

(Use magnifying glass)

1. Jaundice due to common duct stone without complicating cholangitis.
  2. Jaundice due to biliary obstruction by neoplasm, uncomplicated by metastases or cholangitis.
  3. Jaundice due to obstructing neoplasm with metastases to the liver.
  4. Jaundice due to cholangitis with or without stone or neoplasm.
  5. Jaundice due to catarrhal icterus and toxic hepatitis.
  6. Cirrhosis of the liver with jaundice.
  7. Cirrhosis of the liver without jaundice.
  8. Jaundice due to miscellaneous causes.
- Later we shall attempt to clarify the reasons for this grouping.

## METHOD

The method used in the original communication was that of Ammon (1) modified so that the reaction was continued over a 2 hour period at 30°. The values were expressed in cubic millimeters of CO<sub>2</sub> liberated from 7.5 mg. acetyl choline chloride in 1.5 cc. bicarbonate Ringer solution by 0.5 cc. of serum diluted 50 times with bicarbonate Ringer solution. We now use double the volume of serum and substrate solutions and employ only a 1 hour period in order to shorten the determinations and to avoid the flattening out of the activity time curves which sometimes occurred with the more active sera when the 2 hour interval was used. The activity was based on the slope of the linear portion of the curve.

Because of the slight modification in technique since

TABLE II

Serum cholinesterase in cases of jaundice due to biliary obstruction by neoplasm (uncomplicated by metastases or cholangitis)

| Case Number | Sex | Age | Date   | Cholinesterase | Duration of Jaundice at First Determination | Temperature | Hemoglobin % | Icteric Index (Acetone Method) | Cholesterol Ester Partition | Bile in Stools | Bile in Urine | Remarks   |
|-------------|-----|-----|--------|----------------|---|-------------|--------------|--------------------------------|-----------------------------|----------------|---------------|---|
| 20          | M   | 57  | 7/12   | 52             | 3 wks.                                      | 99.         | 94           | 84                             | 350-115                     | 0              | 2+            | Galactose 3.5 gms. Operation 7/16.                                  |
|             |     |     | 7/14   | 66             |   | 99.8        |              | 40                             |                             |                | 2+            | Ca. of pancreas.  |
| 21          | M   | 59  | 11/15  | 65             | 3 days                                      | 99.2        | 91           | 26                             | 250 130                     | 0              | 2+            | Operation 11/19. Ca. of pancreas.                                   |
|             |     |     | *11 25 | 53             |   | 99.2        |              | 6                              |                             |                | 0             |   |
| 22          | F   | 62  | 8/30   | 57             | 3 wks.                                      | 100.4       | 81           | 25                             | 510/215                     | ±              | 2+            | Galactose 4.0 gms. Operation 9/11.                                  |
|             |     |     | 9/3    | 51             |   | 101.8       |              | 35                             |                             |                | 2+            | Carcinoma of common duct.   |
|             |     |     | *9/20  | 41             |   | 100.        |              | 20                             |                             |                | 0             |   |
| 23          | M   | 58  | 1/20   | 19             | 1 wk.                                       | 100.        | 77           | 46                             | 460                         | 0              | 4+            | Galactose 3.5 gms. Operation 2/1. Ca. of pancreas.                  |
| 24          | F   | 55  | 12/12  | 58             | 3 wks.                                      | 99.         | 75           | 25                             | 210/100                     | 0              | 4+            | Phosphatase 35. Operation 12/14.                                    |
|             |     |     | *12/20 | 39             |   | 99.         |              | 20                             |                             |                |               | Ca. of gall bladder. Complete occlusion of common duct.             |
| 25          | M   | 46  | 7/2    | 74             | 10 days                                     | 99.         | 70           | 28                             | 198-75                      | 0              | 4+            | Phosphatase 10.2. Operation 7/10. Ca. of pancreas.                  |
| 26          | F   | 50  | 5/20   | 46             | 3 wks.                                      | 99.2        | 90           | 25                             | 300/150                     |                | 4+            | Operation 4/24. Ca. of pancreas.                                    |
| 27          | F   | 77  | 5/27   | 40             | 3 wks.                                      | 99.         | 73           | 52                             | 273/33                      | ±              | 4+            | Operation 6/1. Ca. of pancreas.                                     |
| 28          | M   | 65  | 7/10   | 43             | 3 mos.                                      | 99.6        | 80           | 55                             | 415/125                     | 0              | 4+            | Galactose 2.3 gms. Phosphatase 84. Operation 7/16. Ca. of pancreas. |

\* Post-operative.

TABLE III

*Serum cholinesterase in cases of jaundice due to obstructing neoplasm with metastases to liver*

| Case Number | Sex | Age | Date  | Cholinesterase | Duration of Jaundice at First Determination | Temperature | Hemoglobin % | Icteric Index (Acetone Method) | Cholesterol Ester Partition | Bile in Stools | Bile in Urine | Remarks  |
|-------------|-----|-----|-------|----------------|---|-------------|--------------|--------------------------------|-----------------------------|----------------|---------------|--|
| 29          | F   | 65  | 12/13 | 37             | 13 days                                     | 98.6        | 63           | 25                             | 320                         | 0              | 2+            | Operation 12/16. Ca. of pancreas. Metastases to liver.   |
| 30          | F   | 53  | 10/28 | 45             | 3 mos.                                      | 100.2       | 85           | 40                             | 135/60                      | 0              | 4+            | Operation 10/31. Ca. of pancreas.  |
|             |     |     | *11/9 | 28             |   | 99.8        |              | 45                             |                             |                | 1+            | Metastases to left lobe of liver.  |
| 31          | M   | 63  | 4/22  | 31             | 23 days                                     | 100.        | 70           | 23                             | 325/165                     | +              | 2+            | Galactose 1.3. Autopsy: Ca. of pancreas with metastases to liver.                                      |
| 32          | F   | 57  | 1/23  | 40             | 6 wks.                                      | 99.4        |              | 48                             | 345/145                     | 0              | 4+            | Palpable mass 3 mos. Metastatic ca. on liver aspiration.   |
| 33          | M   | 69  | 12/20 | 9              | 4 wks.                                      | 99.         | 65.          | 16                             | 155/40                      | +              | 2+            | Phosphatase 4.1. Autopsy: Ca. of pancreas with massive liver metastases.                               |
| 34          | M   | 79  | 12/20 | 13             | 1 mo.                                       | 99.4        |              | 100                            |                             | 0              | 1+            | Phosphatase 3.0. Autopsy: Ca. of gall bladder. Complete occlusion of common duct. Metastases to liver. |
| 35          | F   | 74  | 3/26  | 14             | 3 wks.                                      | 100.        | 100          | 45                             |                             | 0              | 4+            | Operation. Ca. of pancreas with metastases to liver.   |
| 36          | M   | 61  | 6/29  | 58             | 4 wks.                                      | 101.4       | 92           | 40                             | 290/51                      | 0              | 4+            | Autopsy: Ca. of pancreas with extensive liver metastases.  |
|             |     |     | *11/6 | 50             |   | 99.         |              |                                | 230/33                      | 0              | 4+            |  |

\*Post-operative.

TABLE IV

*Serum cholinesterase in cases of jaundice due to cholangitis (with or without stone or neoplasm)*

| Case Number | Sex | Age | Date   | Cholinesterase | Duration of Jaundice at First Determination | Temperature | Hemoglobin % | Icteric Index (Acetone Method) | Cholesterol Ester Partition | Bile in Stools | Bile in Urine | Remarks  |
|-------------|-----|-----|--------|----------------|---|-------------|--------------|--------------------------------|-----------------------------|----------------|---------------|--|
| 37          | F   | 55  | 9/13   | 35             | 14 days                                     | 100.        | 63           | 15                             | 170/50                      | +              | tr.           | Autopsy: Suppurative cholangitis and stones at the papilla Vater.  |
| 38          | F   | 63  | *11/9  | 8              | 6 wks.                                      | 100.6       | 94           | 11                             | 250/95                      | +++            | 3+            | Operation 11/6. Suppurative cholangitis stone at ampulla.  |
|             |     |     | *11/11 | 5              |   | 101.8       |              | 6                              |                             | +              | 1+            |  |
|             |     |     | *11/20 | 6              |   | 101.        |              |                                |                             |                | 0             |  |
|             |     |     | *1/29  | 8              |   |             |              |                                |                             |                |               |  |
| 39          | F   | 60  | 12/19  | 39             | Recurrent attacks 20 mos.                   | 99.         | 55           | 14                             | 260                         | +              | 2+            | Galactose 1.7. Phosphatase 21. Cholangitis and cholangiolitis and biliary cirrhosis on exploration and biopsy. |
|             |     |     | 12/23  | 35             |   | 99.8        |              | 28                             |                             |                | 3+            |  |
| 40          | F   | 54  | 9/24   | 16             | 5 mos.                                      | 101.5       | 55           | 30                             | 670/50                      | 0              | 4+            | Phosphatase 20. Autopsy: Ca. of gall bladder occluding common duct. Cholangiolitis.                            |
| 41          | M   | 35  | *10/25 | 29             | 3½ yrs.                                     | 100.4       | 95           | 20                             | 430/195                     | +              | 3+            | Operation 10/23. Hepatico duodenostomy. Galactose 0.   |
| 42          | M   | 44  | 7/24   | 35             | 2 mos.                                      | 105.        | 90           | 25                             | 600/187                     | 0              | 4+            | Operation 7/26. Ca. of pancreas. Cholangitis.  |
| 43          | M   | 53  | 12/10  | 47             | 1 days                                      | 102.        | 90           | 21                             | 220                         | +              | 3+            | Cholangitis following cholecysto-duodenostomy.   |
|             |     |     | 12/11  | 48             | 12 days                                     | 102.        |              |                                |                             |                |               |  |

\*Post-operative.

our earlier reports, a series of 223 normal controls selected from apparently healthy adults is presented.

Average deviation of a single observation...  $\pm 10.72$

Mean error of a single observation.....  $\pm 13.14$

Probable error of a single observation.....  $\pm 8.88$

Arithmetical Mean

80.3

Average deviation of the arithmetical mean..  $\pm 0.72$

Mean error of the arithmetical mean.....  $\pm 0.88$

Probable error of the arithmetical mean.....  $\pm 0.60$

slightly higher values during the period of observation. It is apparent, from these figures, that a pre-operative value below 40 throws grave doubt on the diagnosis of simple common duct stone. It should be emphasized that this group does not include cases of common duct stone complicated by cholangitis. These will be considered in Group IV.

In 9 cases of obstructive jaundice due to carcinoma—uncomplicated by cholangitis or metastases—6 of the pancreas, 2 of the common duct and 1 of the gall

TABLE V.

SERUM CHOLINESTERASE IN CASES OF JAUNDICE DUE TO CATARRHAL ICTERUS AND TOXIC HEPATITIS.

| CASE NUMBER | SEX | AGE | DATE     | CHOLINESTERASE<br>(U.S. UNITS) AT<br>JAUNDICE AT<br>FIRST DETECT. | TEMPERATURE | HEMOGLOBIN<br>(G.M.) (MILLS.) | (PALATABLE<br>(G.M. EXTRACTED) | TOTAL PROTEIN<br>IN SERUM | ICTERIC INDEX<br>(CALCULATED METHOD) | CHOLESTEROL<br>IN URINE | BILE IN URINE<br>PARTITION | BILE IN STOOL | URIC ACID<br>IN URINE | LIVER AND<br>SPLEEN   | REMARKS   |  |  |
|-------------|-----|-----|----------|---|-------------|-------------------------------|--------------------------------|---------------------------|--------------------------------------|-------------------------|----------------------------|---------------|-----------------------|---|---|--|--|
| 48 M 57     | M   | 57  | 10/14/33 | 23  | 99.5        | 93                            | 6.7                            | 13.5                      | 15                                   | 50/130                  | 0                          | 1/30          | 1/2                   | LIVER EDGE DOWN 1 FINGER<br>SPLEEN NOT PALPABLE                     | TOXIC HEPATITIS. SUBSIDED SLOWLY. LACTIC<br>TOLERANCE TEST SHOWED LIVER DAMAGE. PAIN-<br>LESS JAUNDICE.                                       |  |  |
| 49 M 57     | M   | 57  | 10/23/33 | 33  | 99.6        |                               | 8.5                            | 15                        | 50/110                               |                         |                            |               |                       |   | LIVER EDGE NOT FELT   |  |  |
| 45 M 53     | M   | 53  | 10/23/33 | 13.6  | 99.5        | 125.5                         | 6.3                            | 6.7                       | 31                                   | 102/60                  | 2                          | 1/10          | 1/2                   | LIVER DOWN 1 FINGER   | TYPICAL CATARRHAL JAUNDICE. STOOLS LIGHT<br>BEFORE ADMISSION.   |  |  |
| 46 M 51     | M   | 51  | 10/23/33 | 5.6   | 99.5        | 111.5                         | 5.4                            | 2.3                       | 2                                    | 175/135                 | 1                          | 1/11          | 1/2                   | LIVER AND SPLEEN NOT<br>FELT  | TYPICAL CATARRHAL JAUNDICE. U.I. UPSET<br>12 DAYS PREVIOUSLY. RAPID RECOVERY.   |  |  |
| 47 M 6      | M   | 6   | 4/13/34  | 0   | 101.1       | 51.1                          |                                |                           | 10                                   | 202/125                 | 1                          | 0             | 1/5                   | LIVER DOWN 3 FINGERS<br>SPLEEN DOWN 1 FINGER                        | TYPICAL CATARRHAL JAUNDICE WITH RAPID<br>RECOVERY.  |  |  |
| 48 F 34     | F   | 34  | 10/17/33 | 12.6  | 100.6       | 115.5                         | 5.2                            | 4.2                       | 2                                    | 125/75                  | 0                          | 1             | 1/2                   | LIVER DOWN 2 FINGERS  | TOXIC HEPATITIS. VERY SICK. 65 GRAINS ATO-<br>MAN ERGAS, AD. LETHARGIC ON ADMISSION. COM-<br>PLETE RECOVERY (HAD ERGOTANINE VASOPRESSIN).     |  |  |
| 49 M 24     | M   | 24  | 10/23/33 | 2   | 99.5        | 99.5                          | 0                              | 0                         | 5.5                                  | 6.0                     | 0                          | 1             | 1/11                  | LIVER AND SPLEEN NOT<br>PALPABLE.                                   | TYPICAL CATARRHAL JAUNDICE. VERY SICK ON<br>ADMISSION. BILIRUBIN PRESENT IN URINE. PPD-<br>TUBERCULIN NORMAL.                                 |  |  |
| 50 M 42     | M   | 42  | 10/23/33 | 12.6  | 133.5       | 65                            |                                |                           | 3.5                                  | 4.7                     | 0                          | 277/175       | 1                     | 1/10  | LIVER DOWN 1 FINGERS  | TYPICAL CATARRHAL JAUNDICE. PROTHROMBIN<br>NORMAL ON 9/20. |  |
| 51 M 42     | M   | 42  | 10/23/33 | 12.6  | 133.5       | 65                            |                                |                           | 13.2                                 | 5.1                     | 24                         | 235/145       | 1                     | 1/40  | SPLEEN NOT FELT.  |  |  |
| 52 M 37     | M   | 37  | 10/23/33 | 10.6  | 99.4        | 101                           | 5.1                            |                           | 57                                   | 115/75                  | 0                          | 0             | 1/2                   | LIVER DOWN 1 FINGER<br>SPLEEN DOWN 3 FINGER                         | TYPICAL CATARRHAL JAUNDICE. PROTHROMBIN<br>TIME 7.7. SEDIMENTATION RATE OVER 6 MMS.   |  |  |
| 53 M 42     | M   | 42  | 10/23/33 | 10.6  | 99.4        | 101                           | 5.1                            |                           | 11                                   | 35/125                  | 10                         | 0             | 1/11                  | LIVER AND SPLEEN DOWN<br>3 FINGERS, BACK TO<br>NORMAL SL DISCHARGE. | TYPICAL CATARRHAL JAUNDICE. IN RECOVERING<br>PHASE.   |  |  |
| 54 F 24     | F   | 24  | 10/23/33 | 6.5   | 99.4        | 91                            |                                |                           | 1.5                                  | 0.5                     | 2                          | 135/75        | 1                     | 0   | 1/20  | LIVER AND SPLEEN NOT FELT                                  | CATARRHAL JAUNDICE. CLAY COLORED STOOLS,<br>REFRAC ADMISSION. U.I. OK. |
| 55 M 24     | M   | 24  | 10/23/33 | 15  | 101.2       | 48.3                          | 5.4                            | 4.5                       | 10                                   | 125/75                  | 10                         | 1             | 1/2                   | LIVER DOWN 3 FINGERS<br>SPLEEN DOWN 1 FINGER                        | TOXIC HEPATITIS ONSET. REMISSION PHASE OF<br>PERNITIOUS ANEMIA ON LIVER THERAPY. SILD CASE<br>SLIGHTLY, BUT SEVERE HEMOLYTIC BY CHYM. "CITUS" |  |  |
| 56 M 16     | M   | 16  | 10/23/33 | 12.6  | 99.4        | 99.4                          | 0                              | 0                         | 22                                   | 225/115                 | 0                          | 0             | 1/20                  | LIVER AND SPLEEN NOT FELT   | TOXIC HEPATITIS WITH SLIGHT CASE OF PERNITIOUS<br>ANEMIA.   |  |  |
| 57 M 61     | M   | 61  | 10/23/33 | 19.6  | 99.4        | 35.4                          | 4.2                            | 4.0                       | 0                                    | 230/135                 | 4                          | 0             | 1/2                   | LIVER DOWN 1 FINGER<br>SPLEEN DOWN 1 FINGER                         | TOXIC HEPATITIS. EVOLVING COMPLETE RECOVERY.<br>4 MMS. LATER, LIVER AND SPLEEN ENLARGED.  |  |  |
| 58 M 42     | M   | 42  | 10/23/33 | 3.94  | 100.5       | 43                            |                                |                           | 1                                    | 250/135                 | 35                         | 0             | 1/11                  | LIVER DOWN 1 FINGER<br>SPLEEN DOWN 1 FINGER                         | TOXIC HEPATITIS. DIAPYCNIC ON PROTHAMINE<br>(60 UNITS DAULT).   |  |  |
| 59 M 42     | M   | 42  | 10/23/33 | 4.6   | 99.6        | 67                            |                                |                           | 62                                   | 105/65                  | 4                          | 1             | 1/20                  | LIVER AND SPLEEN NOT<br>PALPABLE.                                   |   |  |  |

(Use magnifying glass)

TABLE VI.

SERUM CHOLINESTERASE IN CASES OF CIRRHOSIS OF THE LIVER WITH JAUNDICE

| CASE NUMBER | SEX | AGE | DATE     | CHOLINESTERASE (U.S. UNITS) AT FIRST DETECT. | TEMPERATURE | HEMOGLOBIN | ALBUMIN (G.M. EXTRACTED) | TOTAL PROTEIN IN SERUM | ICTERIC INDEX IN URINE | BILE IN URINE | BILE IN STOOL | URIC ACID IN URINE | REMARKS   |   |
|-------------|-----|-----|----------|--|-------------|------------|--------------------------|------------------------|------------------------|---------------|---------------|--------------------|---|---|
| 33          | M   | 45  | 10/23/33 | 10   | 99.3        |            |                          |                        |                        |               |               |                    | LIVER FIRM, CAPS TO UMBILICUS, SPLEEN NOT FELT. | 1. AUTOPSY SHOWS LAENEC'S CIRRHOSIS. ALCOHOLIC HISTORY. |
| 34          | M   | 45  | 10/23/33 | 10   | 99.3        |            |                          |                        |                        |               |               |                    | LIVER FIRM, CAPS TO UMBILICUS, SPLEEN NOT FELT. | 2. CLINICALLY TYPICAL CIRRHOSIS WITH HEPATITIS.         |
| 35          | M   | 45  | 10/23/33 | 10   | 99.3        |            |                          |                        |                        |               |               |                    | LIVER FIRM, CAPS TO UMBILICUS, SPLEEN NOT FELT. | 3. CIRRHOSIS PRODUCED BY OPERATING.                     |
| 36          | M   | 45  | 10/23/33 | 10   | 99.3        |            |                          |                        |                        |               |               |                    | LIVER FIRM, CAPS TO UMBILICUS, SPLEEN NOT FELT. | 4. CLINICALLY TYPICAL CIRRHOSIS                         |
| 37          | M   | 45  | 10/23/33 | 10   | 99.3        |            |                          |                        |                        |               |               |                    | LIVER FIRM, CAPS TO UMBILICUS, SPLEEN NOT FELT. | 5. CLINICALLY TYPICAL CIRRHOSIS                         |
| 38          | M   | 45  | 10/23/33 | 10   | 99.3        |            |                          |                        |                        |               |               |                    | LIVER FIRM, CAPS TO UMBILICUS, SPLEEN NOT FELT. | 6. CLINICALLY TYPICAL CIRRHOSIS                         |
| 39          | M   | 45  | 10/23/33 | 10   | 99.3        |            |                          |                        |                        |               |               |                    | LIVER FIRM, CAPS TO UMBILICUS, SPLEEN NOT FELT. | 7. CLINICALLY TYPICAL CIRRHOSIS                         |
| 40          | M   | 45  | 10/23/33 | 10   | 99.3        |            |                          |                        |                        |               |               |                    | LIVER FIRM, CAPS TO UMBILICUS, SPLEEN NOT FELT. | 8. CLINICALLY TYPICAL CIRRHOSIS                         |
| 41          | M   | 45  | 10/23/33 | 10   | 99.3        |            |                          |                        |                        |               |               |                    | LIVER FIRM, CAPS TO UMBILICUS, SPLEEN NOT FELT. | 9. CLINICALLY TYPICAL CIRRHOSIS                         |
| 42          | M   | 45  | 10/23/33 | 10   | 99.3        |            |                          |                        |                        |               |               |                    | LIVER FIRM, CAPS TO UMBILICUS, SPLEEN NOT FELT. | 10. CLINICALLY TYPICAL CIRRHOSIS                        |
| 43          | M   | 45  | 10/23/33 | 10   | 99.3        |            |                          |                        |                        |               |               |                    | LIVER FIRM, CAPS TO UMBILICUS, SPLEEN NOT FELT. | 11. CLINICALLY TYPICAL CIRRHOSIS                        |
| 44          | M   | 45  | 10/23/33 | 10   | 99.3        |            |                          |                        |                        |               |               |                    | LIVER FIRM, CAPS TO UMBILICUS, SPLEEN NOT FELT. | 12. CLINICALLY TYPICAL CIRRHOSIS                        |
| 45          | M   | 45  | 10/23/33 | 10   | 99.3        |            |                          |                        |                        |               |               |                    | LIVER FIRM, CAPS TO UMBILICUS, SPLEEN NOT FELT. | 13. CLINICALLY TYPICAL CIRRHOSIS                        |
| 46          | M   | 45  | 10/23/33 | 10   | 99.3        |            |                          |                        |                        |               |               |                    | LIVER FIRM, CAPS TO UMBILICUS, SPLEEN NOT FELT. | 14. CLINICALLY TYPICAL CIRRHOSIS                        |
| 47          | M   | 45  | 10/23/33 | 10   | 99.3        |            |                          |                        |                        |               |               |                    | LIVER FIRM, CAPS TO UMBILICUS, SPLEEN NOT FELT. | 15. CLINICALLY TYPICAL CIRRHOSIS                        |
| 48          | M   | 45  | 10/23/33 | 10   | 99.3        |            |                          |                        |                        |               |               |                    | LIVER FIRM, CAPS TO UMBILICUS, SPLEEN NOT FELT. | 16. CLINICALLY TYPICAL CIRRHOSIS                        |
| 49          | M   | 45  | 10/23/33 | 10   | 99.3        |            |                          |                        |                        |               |               |                    | LIVER FIRM, CAPS TO UMBILICUS, SPLEEN NOT FELT. | 17. CLINICALLY TYPICAL CIRRHOSIS                        |
| 50          | M   | 45  | 10/23/33 | 10   | 99.3        |            |                          |                        |                        |               |               |                    | LIVER FIRM, CAPS TO UMBILICUS, SPLEEN NOT FELT. | 18. CLINICALLY TYPICAL CIRRHOSIS                        |
| 51          | M   | 45  | 10/23/33 | 10   | 99.3        |            |                          |                        |                        |               |               |                    | LIVER FIRM, CAPS TO UMBILICUS, SPLEEN NOT FELT. | 19. CLINICALLY TYPICAL CIRRHOSIS                        |
| 52          | M   | 45  | 10/23/33 | 10   | 99.3        |            |                          |                        |                        |               |               |                    | LIVER FIRM, CAPS TO UMBILICUS, SPLEEN NOT FELT. | 20. CLINICALLY TYPICAL CIRRHOSIS                        |
| 53          | M   | 45  | 10/23/33 | 10   | 99.3        |            |                          |                        |                        |               |               |                    | LIVER FIRM, CAPS TO UMBILICUS, SPLEEN NOT FELT. | 21. CLINICALLY TYPICAL CIRRHOSIS                        |
| 54          | M   | 45  | 10/23/33 | 10   | 99.3        |            |                          |                        |                        |               |               |                    | LIVER FIRM, CAPS TO UMBILICUS, SPLEEN NOT FELT. | 22. CLINICALLY TYPICAL CIRRHOSIS                        |
| 55          | M   | 45  | 10/23/33 | 10   | 99.3        |            |                          |                        |                        |               |               |                    | LIVER FIRM, CAPS TO UMBILICUS, SPLEEN NOT FELT. | 23. CLINICALLY TYPICAL CIRRHOSIS                        |
| 56          | M   | 45  | 10/23/33 | 10   | 99.3        |            |                          |                        |                        |               |               |                    | LIVER FIRM, CAPS TO UMBILICUS, SPLEEN NOT FELT. | 24. CLINICALLY TYPICAL CIRRHOSIS                        |
| 57          | M   | 45  | 10/23/33 | 10   | 99.3        |            |                          |                        |                        |               |               |                    | LIVER FIRM, CAPS TO UMBILICUS, SPLEEN NOT FELT. | 25. CLINICALLY TYPICAL CIRRHOSIS                        |
| 58          | M   | 45  | 10/23/33 | 10   | 99.3        |            |                          |                        |                        |               |               |                    | LIVER FIRM, CAPS TO UMBILICUS, SPLEEN NOT FELT. | 26. CLINICALLY TYPICAL CIRRHOSIS                        |
| 59          | M   | 45  | 10/23/33 | 10   | 99.3        |            |                          |                        |                        |               |               |                    | LIVER FIRM, CAPS TO UMBILICUS, SPLEEN NOT FELT. | 27. CLINICALLY TYPICAL CIRRHOSIS                        |
| 60          | M   | 45  | 10/23/33 | 10   | 99.3        |            |                          |                        |                        |               |               |                    | LIVER FIRM, CAPS TO UMBILICUS, SPLEEN NOT FELT. | 28. CLINICALLY TYPICAL CIRRHOSIS                        |
| 61          | M   | 45  | 10/23/33 | 10   | 99.3        |            |                          |                        |                        |               |               |                    | LIVER FIRM, CAPS TO UMBILICUS, SPLEEN NOT FELT. | 29. CLINICALLY TYPICAL CIRRHOSIS                        |
| 62          | M   | 45  | 10/23/33 | 10   | 99.3        |            |                          |                        |                        |               |               |                    | LIVER FIRM, CAPS TO UMBILICUS, SPLEEN NOT FELT. | 30. CLINICALLY TYPICAL CIRRHOSIS                        |
| 63          | M   | 45  | 10/23/33 | 10   | 99.3        |            |                          |                        |                        |               |               |                    | LIVER FIRM, CAPS TO UMBILICUS, SPLEEN NOT FELT. | 31. CLINICALLY TYPICAL CIRRHOSIS                        |
| 64          | M   | 45  | 10/23/33 | 10   | 99.3        |            |                          |                        |                        |               |               |                    | LIVER FIRM, CAPS TO UMBILICUS, SPLEEN NOT FELT. | 32. CLINICALLY TYPICAL CIRRHOSIS                        |
| 65          | M   | 45  | 10/23/33 | 10   | 99.3        |            |                          |                        |                        |               |               |                    | LIVER FIRM, CAPS TO UMBILICUS, SPLEEN NOT FELT. | 33. CLINICALLY TYPICAL CIRRHOSIS                        |
| 66          | M   | 45  | 10/23/33 | 10   | 99.3        |            |                          |                        |                        |               |               |                    | LIVER FIRM, CAPS TO UMBILICUS, SPLEEN NOT FELT. | 34. CLINICALLY TYPICAL CIRRHOSIS                        |
| 67          | M   | 45  | 10/23/33 | 10   | 99.3        |            |                          |                        |                        |               |               |                    | LIVER FIRM, CAPS TO UMBILICUS, SPLEEN NOT FELT. | 35. CLINICALLY TYPICAL CIRRHOSIS                        |
| 68          | M   | 45  | 10/23/33 | 10   | 99.3        |            |                          |                        |                        |               |               |                    | LIVER FIRM, CAPS TO UMBILICUS, SPLEEN NOT FELT. | 36. CLINICALLY TYPICAL CIRRHOSIS                        |
| 69          | M   | 45  | 10/23/33 | 10   | 99.3        |            |                          |                        |                        |               |               |                    | LIVER FIRM, CAPS TO UMBILICUS, SPLEEN NOT FELT. | 37. CLINICALLY TYPICAL CIRRHOSIS                        |
| 70          | M   | 45  | 10/23/33 | 10   | 99.3        |            |                          |                        |                        |               |               |                    | LIVER FIRM, CAPS TO UMBILICUS, SPLEEN NOT FELT. | 38. CLINICALLY TYPICAL CIRRHOSIS                        |
| 71          | M   | 45  | 10/23/33 | 10   | 99.3        |            |                          |                        |                        |               |               |                    | LIVER FIRM, CAPS TO UMBILICUS, SPLEEN NOT FELT. | 39. CLINICALLY TYPICAL CIRRHOSIS                        |
| 72          | M   | 45  | 10/23/33 | 10   | 99.3        |            |                          |                        |                        |               |               |                    | LIVER FIRM, CAPS TO UMBILICUS, SPLEEN NOT FELT. | 40. CLINICALLY TYPICAL CIRRHOSIS                        |
| 73          | M   | 45  | 10/23/33 | 10   | 99.3        |            |                          |                        |                        |               |               |                    | LIVER FIRM, CAPS TO UMBILICUS, SPLEEN NOT FELT. | 41. CLINICALLY TYPICAL CIRRHOSIS                        |
| 74          | M   | 45  | 10/23/33 | 10   | 99.3        |            |                          |                        |                        |               |               |                    | LIVER FIRM, CAPS TO UMBILICUS, SPLEEN NOT FELT. | 42. CLINICALLY TYPICAL CIRRHOSIS                        |



were associated with massive metastases, and in case 33, the necropsy showed almost complete replacement of liver tissue. Case 36 with cholinesterase values of 50 and 58 also presented extensive metastases at post-mortem.

The 7 cases of cholangitis with jaundice included 2 due to stone found at the papilla of Vater, one in which the common duct had not been found at operation, but in which biopsy of the liver showed acute cholangitis; one secondary to an old traumatic

followed through the entire course of their disease with observations at intervals during the icteric state and, after recovery, in the non-icteric state. Case 44 presented values of 28, 33, 34 during the icteric state, rising to 44, 55 and 67 in the 6 weeks following the disappearance of jaundice. Case 45 showed readings of 62, 65 and 56 during the jaundiced state, rising to 95 two months after the disappearance of the jaundice. Case 48 showed values of 82, 84, 77 and 100 while jaundiced, and four months later, 100. Case 50 showed

TABLE VII  
SERUM CHOLINESTERASE IN CASES OF DISEASE OF THE LIVER WITHOUT JAUNDICE

| CASE NUMBER | AGE | SEX | DATE | CHOLINESTERASE (UNIT, COLETTES) | TEMPERATURE | HEMAGLOBIN | HAEMATOCRIT (%) | RED BLOOD CELLS (MILLION) | WHITE BLOOD CELLS (MILLION) | PLATELETS (MILLION) | ALBUMIN (G) | GLOBULIN (G) | TOTAL PROTEIN (G) | CHOLINESTERASE (UNIT, COLETTES) | REMARKS |                            |  |
|-------------|-----|-----|------|---------------------------------|-------------|------------|-----------------|---------------------------|-----------------------------|---------------------|-------------|--------------|-------------------|---------------------------------|---------|----------------------------|--|
| 23          | 45  | F   | 9/17 | 45                              | 99.5        | 67         | 2.1             | 5.1                       | 8                           | 40                  | 12.7        | 1.2          | 13.9              | 257/142                         | NONE    | LIVER TEND, DOWN 2 FINGERS | D JAUNDICE, WITH PAIN 2 WEEKS, EARLIER.            |
| 24          | 45  | F   | 9/17 | 24                              | 99.5        | 67         | 2.1             | 5.1                       | 8                           | 40                  | 12.7        | 1.2          | 13.9              | 257/142                         | PRESENT | LIVER TEND, DOWN 2 FINGERS | D BILIRUBIN SHOWN, ESRICH, ALBUMIN CHOLINESTERASE. |
| 25          | 45  | F   | 9/17 | 25                              | 99.5        | 67         | 2.1             | 5.1                       | 8                           | 40                  | 12.7        | 1.2          | 13.9              | 257/142                         | NONE    | LIVER TEND, DOWN 2 FINGERS | D BILIRUBIN SHOWN, ESRICH, ALBUMIN CHOLINESTERASE. |
| 26          | 45  | F   | 9/17 | 26                              | 99.5        | 67         | 2.1             | 5.1                       | 8                           | 40                  | 12.7        | 1.2          | 13.9              | 257/142                         | PRESENT | LIVER TEND, DOWN 2 FINGERS | D BILIRUBIN SHOWN, ESRICH, ALBUMIN CHOLINESTERASE. |
| 27          | 45  | F   | 9/17 | 27                              | 99.5        | 67         | 2.1             | 5.1                       | 8                           | 40                  | 12.7        | 1.2          | 13.9              | 257/142                         | NONE    | LIVER TEND, DOWN 2 FINGERS | D BILIRUBIN SHOWN, ESRICH, ALBUMIN CHOLINESTERASE. |
| 28          | 45  | F   | 9/17 | 28                              | 99.5        | 67         | 2.1             | 5.1                       | 8                           | 40                  | 12.7        | 1.2          | 13.9              | 257/142                         | PRESENT | LIVER TEND, DOWN 2 FINGERS | D BILIRUBIN SHOWN, ESRICH, ALBUMIN CHOLINESTERASE. |
| 29          | 45  | F   | 9/17 | 29                              | 99.5        | 67         | 2.1             | 5.1                       | 8                           | 40                  | 12.7        | 1.2          | 13.9              | 257/142                         | NONE    | LIVER TEND, DOWN 2 FINGERS | D BILIRUBIN SHOWN, ESRICH, ALBUMIN CHOLINESTERASE. |
| 30          | 45  | F   | 9/17 | 30                              | 99.5        | 67         | 2.1             | 5.1                       | 8                           | 40                  | 12.7        | 1.2          | 13.9              | 257/142                         | PRESENT | LIVER TEND, DOWN 2 FINGERS | D BILIRUBIN SHOWN, ESRICH, ALBUMIN CHOLINESTERASE. |
| 31          | 45  | F   | 9/17 | 31                              | 99.5        | 67         | 2.1             | 5.1                       | 8                           | 40                  | 12.7        | 1.2          | 13.9              | 257/142                         | NONE    | LIVER TEND, DOWN 2 FINGERS | D BILIRUBIN SHOWN, ESRICH, ALBUMIN CHOLINESTERASE. |
| 32          | 45  | F   | 9/17 | 32                              | 99.5        | 67         | 2.1             | 5.1                       | 8                           | 40                  | 12.7        | 1.2          | 13.9              | 257/142                         | PRESENT | LIVER TEND, DOWN 2 FINGERS | D BILIRUBIN SHOWN, ESRICH, ALBUMIN CHOLINESTERASE. |
| 33          | 45  | F   | 9/17 | 33                              | 99.5        | 67         | 2.1             | 5.1                       | 8                           | 40                  | 12.7        | 1.2          | 13.9              | 257/142                         | NONE    | LIVER TEND, DOWN 2 FINGERS | D BILIRUBIN SHOWN, ESRICH, ALBUMIN CHOLINESTERASE. |
| 34          | 45  | F   | 9/17 | 34                              | 99.5        | 67         | 2.1             | 5.1                       | 8                           | 40                  | 12.7        | 1.2          | 13.9              | 257/142                         | PRESENT | LIVER TEND, DOWN 2 FINGERS | D BILIRUBIN SHOWN, ESRICH, ALBUMIN CHOLINESTERASE. |
| 35          | 45  | F   | 9/17 | 35                              | 99.5        | 67         | 2.1             | 5.1                       | 8                           | 40                  | 12.7        | 1.2          | 13.9              | 257/142                         | NONE    | LIVER TEND, DOWN 2 FINGERS | D BILIRUBIN SHOWN, ESRICH, ALBUMIN CHOLINESTERASE. |
| 36          | 45  | F   | 9/17 | 36                              | 99.5        | 67         | 2.1             | 5.1                       | 8                           | 40                  | 12.7        | 1.2          | 13.9              | 257/142                         | PRESENT | LIVER TEND, DOWN 2 FINGERS | D BILIRUBIN SHOWN, ESRICH, ALBUMIN CHOLINESTERASE. |
| 37          | 45  | F   | 9/17 | 37                              | 99.5        | 67         | 2.1             | 5.1                       | 8                           | 40                  | 12.7        | 1.2          | 13.9              | 257/142                         | NONE    | LIVER TEND, DOWN 2 FINGERS | D BILIRUBIN SHOWN, ESRICH, ALBUMIN CHOLINESTERASE. |
| 38          | 45  | F   | 9/17 | 38                              | 99.5        | 67         | 2.1             | 5.1                       | 8                           | 40                  | 12.7        | 1.2          | 13.9              | 257/142                         | PRESENT | LIVER TEND, DOWN 2 FINGERS | D BILIRUBIN SHOWN, ESRICH, ALBUMIN CHOLINESTERASE. |
| 39          | 45  | F   | 9/17 | 39                              | 99.5        | 67         | 2.1             | 5.1                       | 8                           | 40                  | 12.7        | 1.2          | 13.9              | 257/142                         | NONE    | LIVER TEND, DOWN 2 FINGERS | D BILIRUBIN SHOWN, ESRICH, ALBUMIN CHOLINESTERASE. |
| 40          | 45  | F   | 9/17 | 40                              | 99.5        | 67         | 2.1             | 5.1                       | 8                           | 40                  | 12.7        | 1.2          | 13.9              | 257/142                         | PRESENT | LIVER TEND, DOWN 2 FINGERS | D BILIRUBIN SHOWN, ESRICH, ALBUMIN CHOLINESTERASE. |
| 41          | 45  | F   | 9/17 | 41                              | 99.5        | 67         | 2.1             | 5.1                       | 8                           | 40                  | 12.7        | 1.2          | 13.9              | 257/142                         | NONE    | LIVER TEND, DOWN 2 FINGERS | D BILIRUBIN SHOWN, ESRICH, ALBUMIN CHOLINESTERASE. |
| 42          | 45  | F   | 9/17 | 42                              | 99.5        | 67         | 2.1             | 5.1                       | 8                           | 40                  | 12.7        | 1.2          | 13.9              | 257/142                         | PRESENT | LIVER TEND, DOWN 2 FINGERS | D BILIRUBIN SHOWN, ESRICH, ALBUMIN CHOLINESTERASE. |
| 43          | 45  | F   | 9/17 | 43                              | 99.5        | 67         | 2.1             | 5.1                       | 8                           | 40                  | 12.7        | 1.2          | 13.9              | 257/142                         | NONE    | LIVER TEND, DOWN 2 FINGERS | D BILIRUBIN SHOWN, ESRICH, ALBUMIN CHOLINESTERASE. |
| 44          | 45  | F   | 9/17 | 44                              | 99.5        | 67         | 2.1             | 5.1                       | 8                           | 40                  | 12.7        | 1.2          | 13.9              | 257/142                         | PRESENT | LIVER TEND, DOWN 2 FINGERS | D BILIRUBIN SHOWN, ESRICH, ALBUMIN CHOLINESTERASE. |
| 45          | 45  | F   | 9/17 | 45                              | 99.5        | 67         | 2.1             | 5.1                       | 8                           | 40                  | 12.7        | 1.2          | 13.9              | 257/142                         | NONE    | LIVER TEND, DOWN 2 FINGERS | D BILIRUBIN SHOWN, ESRICH, ALBUMIN CHOLINESTERASE. |
| 46          | 45  | F   | 9/17 | 46                              | 99.5        | 67         | 2.1             | 5.1                       | 8                           | 40                  | 12.7        | 1.2          | 13.9              | 257/142                         | PRESENT | LIVER TEND, DOWN 2 FINGERS | D BILIRUBIN SHOWN, ESRICH, ALBUMIN CHOLINESTERASE. |
| 47          | 45  | F   | 9/17 | 47                              | 99.5        | 67         | 2.1             | 5.1                       | 8                           | 40                  | 12.7        | 1.2          | 13.9              | 257/142                         | NONE    | LIVER TEND, DOWN 2 FINGERS | D BILIRUBIN SHOWN, ESRICH, ALBUMIN CHOLINESTERASE. |
| 48          | 45  | F   | 9/17 | 48                              | 99.5        | 67         | 2.1             | 5.1                       | 8                           | 40                  | 12.7        | 1.2          | 13.9              | 257/142                         | PRESENT | LIVER TEND, DOWN 2 FINGERS | D BILIRUBIN SHOWN, ESRICH, ALBUMIN CHOLINESTERASE. |
| 49          | 45  | F   | 9/17 | 49                              | 99.5        | 67         | 2.1             | 5.1                       | 8                           | 40                  | 12.7        | 1.2          | 13.9              | 257/142                         | NONE    | LIVER TEND, DOWN 2 FINGERS | D BILIRUBIN SHOWN, ESRICH, ALBUMIN CHOLINESTERASE. |
| 50          | 45  | F   | 9/17 | 50                              | 99.5        | 67         | 2.1             | 5.1                       | 8                           | 40                  | 12.7        | 1.2          | 13.9              | 257/142                         | PRESENT | LIVER TEND, DOWN 2 FINGERS | D BILIRUBIN SHOWN, ESRICH, ALBUMIN CHOLINESTERASE. |

(Use magnifying glass)

TABLE VIII  
SERUM CHOLINESTERASE IN CASES OF JAUNDICE DUE TO INTESTINAL CAUSES

| CASE NUMBER | AGE | SEX | DATE | CHOLINESTERASE | TEMPERATURE | HEMAGLOBIN & HAEMATOCRIT | RED BLOOD CELLS | WHITE BLOOD CELLS | PLATELETS | ALBUMIN | GLOBULIN | TOTAL PROTEIN | CHOLINESTERASE | REMARKS |         |                            |  |
|-------------|-----|-----|------|----------------|-------------|--------------------------|-----------------|-------------------|-----------|---------|----------|---------------|----------------|---------|---------|----------------------------|--|
| 51          | 45  | F   | 9/17 | 51             | 99.5        | 67                       | 2.1             | 5.1               | 8         | 40      | 12.7     | 1.2           | 13.9           | 257/142 | NONE    | LIVER TEND, DOWN 2 FINGERS | D BILIRUBIN SHOWN, ESRICH, ALBUMIN CHOLINESTERASE. |
| 52          | 45  | F   | 9/17 | 52             | 99.5        | 67                       | 2.1             | 5.1               | 8         | 40      | 12.7     | 1.2           | 13.9           | 257/142 | PRESENT | LIVER TEND, DOWN 2 FINGERS | D BILIRUBIN SHOWN, ESRICH, ALBUMIN CHOLINESTERASE. |
| 53          | 45  | F   | 9/17 | 53             | 99.5        | 67                       | 2.1             | 5.1               | 8         | 40      | 12.7     | 1.2           | 13.9           | 257/142 | NONE    | LIVER TEND, DOWN 2 FINGERS | D BILIRUBIN SHOWN, ESRICH, ALBUMIN CHOLINESTERASE. |
| 54          | 45  | F   | 9/17 | 54             | 99.5        | 67                       | 2.1             | 5.1               | 8         | 40      | 12.7     | 1.2           | 13.9           | 257/142 | PRESENT | LIVER TEND, DOWN 2 FINGERS | D BILIRUBIN SHOWN, ESRICH, ALBUMIN CHOLINESTERASE. |
| 55          | 45  | F   | 9/17 | 55             | 99.5        | 67                       | 2.1             | 5.1               | 8         | 40      | 12.7     | 1.2           | 13.9           | 257/142 | NONE    | LIVER TEND, DOWN 2 FINGERS | D BILIRUBIN SHOWN, ESRICH, ALBUMIN CHOLINESTERASE. |
| 56          | 45  | F   | 9/17 | 56             | 99.5        | 67                       | 2.1             | 5.1               | 8         | 40      | 12.7     | 1.2           | 13.9           | 257/142 | PRESENT | LIVER TEND, DOWN 2 FINGERS | D BILIRUBIN SHOWN, ESRICH, ALBUMIN CHOLINESTERASE. |
| 57          | 45  | F   | 9/17 | 57             | 99.5        | 67                       | 2.1             | 5.1               | 8         | 40      | 12.7     | 1.2           | 13.9           | 257/142 | NONE    | LIVER TEND, DOWN 2 FINGERS | D BILIRUBIN SHOWN, ESRICH, ALBUMIN CHOLINESTERASE. |
| 58          | 45  | F   | 9/17 | 58             | 99.5        | 67                       | 2.1             | 5.1               | 8         | 40      | 12.7     | 1.2           | 13.9           | 257/142 | PRESENT | LIVER TEND, DOWN 2 FINGERS | D BILIRUBIN SHOWN, ESRICH, ALBUMIN CHOLINESTERASE. |
| 59          | 45  | F   | 9/17 | 59             | 99.5        | 67                       | 2.1             | 5.1               | 8         | 40      | 12.7     | 1.2           | 13.9           | 257/142 | NONE    | LIVER TEND, DOWN 2 FINGERS | D BILIRUBIN SHOWN, ESRICH, ALBUMIN CHOLINESTERASE. |
| 60          | 45  | F   | 9/17 | 60             | 99.5        | 67                       | 2.1             | 5.1               | 8         | 40      | 12.7     | 1.2           | 13.9           | 257/142 | PRESENT | LIVER TEND, DOWN 2 FINGERS | D BILIRUBIN SHOWN, ESRICH, ALBUMIN CHOLINESTERASE. |
| 61          | 45  | F   | 9/17 | 61             | 99.5        | 67                       | 2.1             | 5.1               | 8         | 40      | 12.7     | 1.2           | 13.9           | 257/142 | NONE    | LIVER TEND, DOWN 2 FINGERS | D BILIRUBIN SHOWN, ESRICH, ALBUMIN CHOLINESTERASE. |
| 62          | 45  | F   | 9/17 | 62             | 99.5        | 67                       | 2.1             | 5.1               | 8         | 40      | 12.7     | 1.2           | 13.9           | 257/142 | PRESENT | LIVER TEND, DOWN 2 FINGERS | D BILIRUBIN SHOWN, ESRICH, ALBUMIN CHOLINESTERASE. |
| 63          | 45  | F   | 9/17 | 63             | 99.5        | 67                       | 2.1             | 5.1               | 8         | 40      | 12.7     | 1.2           | 13.9           | 257/142 | NONE    | LIVER TEND, DOWN 2 FINGERS | D BILIRUBIN SHOWN, ESRICH, ALBUMIN CHOLINESTERASE. |
| 64          | 45  | F   | 9/17 | 64             | 99.5        | 67                       | 2.1             | 5.1               | 8         | 40      | 12.7     | 1.2           | 13.9           | 257/142 | PRESENT | LIVER TEND, DOWN 2 FINGERS | D BILIRUBIN SHOWN, ESRICH, ALBUMIN CHOLINESTERASE. |
| 65          | 45  | F   | 9/17 | 65             | 99.5        | 67                       | 2.1             | 5.1               | 8         | 40      | 12.7     | 1.2           | 13.9           | 257/142 | NONE    | LIVER TEND, DOWN 2 FINGERS | D BILIRUBIN SHOWN, ESRICH, ALBUMIN CHOLINESTERASE. |
| 66          | 45  | F   | 9/17 | 66             | 99.5        | 67                       | 2.1             | 5.1               | 8         | 40      | 12.7     | 1.2           | 13.9           | 257/142 | PRESENT | LIVER TEND, DOWN 2 FINGERS | D BILIRUBIN SHOWN, ESRICH, ALBUMIN CHOLINESTERASE. |
| 67          | 45  | F   | 9/17 | 67             | 99.5        | 67                       | 2.1             | 5.1               | 8         | 40      | 12.7     | 1.2           | 13.9           | 257/142 | NONE    | LIVER TEND, DOWN 2 FINGERS | D BILIRUBIN SHOWN, ESRICH, ALBUMIN CHOLINESTERASE. |
| 68          | 45  | F   | 9/17 | 68             | 99.5        | 67                       | 2.1             | 5.1               | 8         | 40      | 12.7     | 1.2           | 13.9           | 257/142 | PRESENT | LIVER TEND, DOWN 2 FINGERS | D BILIRUBIN SHOWN, ESRICH, ALBUMIN CHOLINESTERASE. |
| 69          | 45  | F   | 9/17 | 69             | 99.5        | 67                       | 2.1             | 5.1               | 8         | 40      | 12.7     | 1.2           | 13.9           | 257/142 | NONE    | LIVER TEND, DOWN 2 FINGERS | D BILIRUBIN SHOWN, ESRICH, ALBUMIN CHOLINESTERASE. |
| 70          | 45  | F   | 9/17 | 70             | 99.5        | 67                       | 2.1             | 5.1               | 8         | 40      | 12.7     | 1.2           | 13.9           | 257/142 | PRESENT | LIVER TEND, DOWN 2 FINGERS | D BILIRUBIN SHOWN, ESRICH, ALBUMIN CHOLINESTERASE. |
| 71          | 45  | F   | 9/17 | 71             | 99.5        | 67                       | 2.1             | 5.1               | 8         | 40      | 12.7     | 1.2           | 13.9           | 257/142 | NONE    | LIVER TEND, DOWN 2 FINGERS | D BILIRUBIN SHOWN, ESRICH, ALBUMIN CHOLINESTERASE. |
| 72          | 45  | F   | 9/17 | 72             | 99.5        | 67                       | 2.1             | 5.1               | 8         | 40      | 12.7     | 1.2           | 13.9           | 257/142 | PRESENT | LIVER TEND, DOWN 2 FINGERS | D BILIRUBIN SHOWN, ESRICH, ALBUMIN CHOLINESTERASE. |
| 73          | 45  | F   | 9/17 | 73             | 99.5        | 67                       | 2.1             | 5.1               | 8         | 40      | 12.7     | 1.2           | 13.9           | 257/142 | NONE    | LIVER TEND, DOWN 2 FINGERS | D BILIRUBIN SHOWN, ESRICH, ALBUMIN CHOLINESTERASE. |
| 74          | 45  | F   | 9/17 | 74             | 99.5        | 67                       | 2.1             | 5.1               | 8         | 40      | 12.7     | 1.2           | 13.9           | 257/142 | PRESENT | LIVER TEND, DOWN 2 FINGERS | D BILIRUBIN SHOWN, ESRICH, ALBUMIN CHOLINESTERASE. |
| 75          | 45  | F   | 9/17 | 75             | 99.5        | 67                       | 2.1             | 5.1               | 8         | 40      | 12.7     | 1.2           | 13.9           | 257/142 | NONE    | LIVER TEND, DOWN 2 FINGERS | D BILIRUBIN SHOWN, ESRICH, ALBUMIN CHOLINESTERASE. |
| 76          | 45  | F   | 9/17 | 76             | 99.5        | 67                       | 2.1             | 5.1               | 8         | 40      | 12.7     | 1.2           | 13.9           | 257/142 | PRESENT | LIVER TEND, DOWN 2 FINGERS | D BILIRUBIN SHOWN, ESRICH, ALBUMIN CHOLINESTERASE. |
| 77          | 45  | F   | 9/17 | 77             | 99.5        | 67                       | 2.1             | 5.1               | 8         | 40      | 12.7     | 1.2           | 13.9           | 257/142 | NONE    | LIVER TEND, DOWN 2 FINGERS | D BILIRUBIN SHOWN, ESRICH, ALBUMIN CHOLINESTERASE. |
| 78          | 45  | F   | 9/17 | 78             | 99.5        | 67                       | 2.1             | 5.1               | 8         | 40      | 12.7     | 1.2           | 13.9           | 257/142 | PRESENT | LIVER TEND, DOWN 2 FINGERS | D BILIRUBIN SHOWN, ESRICH, ALBUMIN CHOLINESTERASE. |
| 79          | 45  | F   | 9/17 | 79             | 99.5        | 67                       | 2.1             | 5.1               | 8         | 40      | 12.7     | 1.2           | 13.9           | 257/142 | NONE    | LIVER TEND, DOWN 2 FINGERS | D BILIRUBIN SHOWN, ESRICH, ALBUMIN CHOLINESTERASE. |
| 80          | 45  | F   | 9/17 | 80             | 99.5        | 67                       | 2.1             | 5.1               | 8         | 40      | 12.7     | 1.2           | 13.9           | 257/142 | PRESENT | LIVER TEND, DOWN 2 FINGERS | D BILIRUBIN SHOWN, ESRICH, ALBUMIN CHOLINESTERASE. |
| 81          | 45  | F   | 9/17 | 81             | 99.5        | 67                       | 2.1             | 5.1               | 8         | 40      | 12.7     | 1.2           | 13.9           | 257/142 | NONE    | LIVER TEND, DOWN 2 FINGERS | D BILIRUBIN SHOWN, ESRICH, ALBUMIN CHOLINESTERASE. |
| 82          | 45  | F   | 9/17 | 82             | 99.5        | 67                       | 2.1             | 5.1               | 8         | 40      | 12.7     | 1.2           | 13.9           | 257/142 | PRESENT | LIVER TEND, DOWN 2 FINGERS | D BILIRUBIN SHOWN, ESRICH, ALBUMIN CHOLINESTERASE. |
| 83          | 45  | F   | 9/17 | 83             | 99.5        | 67                       | 2.1             | 5.1               | 8         | 40      | 12.7     | 1.2           | 13.9           | 257/142 | NONE    | LIVER TEND, DOWN 2 FINGERS | D BILIRUBIN SHOWN, ESRICH, ALBUMIN CHOLINESTERASE. |
| 84          | 45  | F   | 9/17 | 84             | 99.5        | 67                       | 2.1             | 5.1               | 8         | 40      | 12.7     | 1.2           | 13.9           | 257/142 | PRESENT | LIVER TEND, DOWN 2 FINGERS | D BILIRUBIN SHOWN, ESRICH, ALBUMIN CHOLINESTERASE. |
| 85          | 45  | F   | 9/17 | 85             | 99.5        | 67                       | 2.1             | 5.1               | 8         | 40      | 12.7     | 1.2           | 13.9           | 257/142 | NONE    | LIVER TEND, DOWN 2 FINGERS | D BILIRUBIN SHOWN, ESRICH, ALBUMIN CHOLINESTERASE. |
| 86          | 45  | F   | 9/17 | 86             | 99.5        | 67                       | 2.1             | 5.1               | 8         | 40      | 12.7     | 1.2           | 13.9           | 257/142 | PRESENT | LIVER TEND, DOWN 2 FINGERS | D BILIRUBIN SHOWN, ESRICH, ALBUMIN CHOLINESTERASE. |
| 87          | 45  | F   | 9/17 | 87             | 99.5        | 67                       | 2.1             | 5.1               | 8         | 40      | 12.7     | 1.2           | 13.9           | 257/142 | NONE    | LIVER TEND, DOWN 2 FINGERS | D BILIRUBIN SHOWN, ESRICH, ALBUMIN CHOLINESTERASE. |
| 88          | 45  | F   | 9/17 | 88             | 99.5        | 67                       | 2.1             | 5.1               | 8         | 40      | 12.7     | 1.2           | 13.9           | 257/142 | PRESENT | LIVER TEND, DOWN 2 FINGERS | D BILIRUBIN SHOWN, ESRICH, ALBUMIN CHOLINESTERASE. |
| 89          | 45  | F   | 9/17 | 89             | 99.5        | 67                       | 2.1             | 5.1               | 8         | 40      | 12.7     | 1.2           | 13.9           | 257/142 | NONE    | LIVER TEND, DOWN 2 FINGERS | D BILIRUBIN SHOWN, ESRICH, ALBUMIN CHOLINESTERASE. |

Thirty-one cases of cirrhosis of the liver were studied, 4 proven by biopsy or operation, 7 by post-mortem, the remaining 20 on grounds considered clinically adequate. Any case about which doubt of the diagnosis might have been entertained was excluded from this series. Reference to Table VI shows that all had hepatomegaly or nodular livers, 13 had ascites, and the others, combinations of associated splenomegaly, marked alcoholic history, esophageal varices or history of antecedent jaundice. Thirty-eight cholinesterase determinations were performed, 13 on 8 patients with jaundice, 23 on patients not icteric at the time the specimens were drawn. The figures varied from 9 to 69, only 2 were above 50 and 4 between 40 and 50. None of the patients with cirrhosis and jaundice showed values above 40.

In Table VIII are listed 8 miscellaneous cases, 1 of acquired hemolytic icterus, 2 of jaundice in the course of sulfanilamide therapy, 1 jaundice in severe per-

mation in the differential diagnosis of liver disease and the jaundiced state.

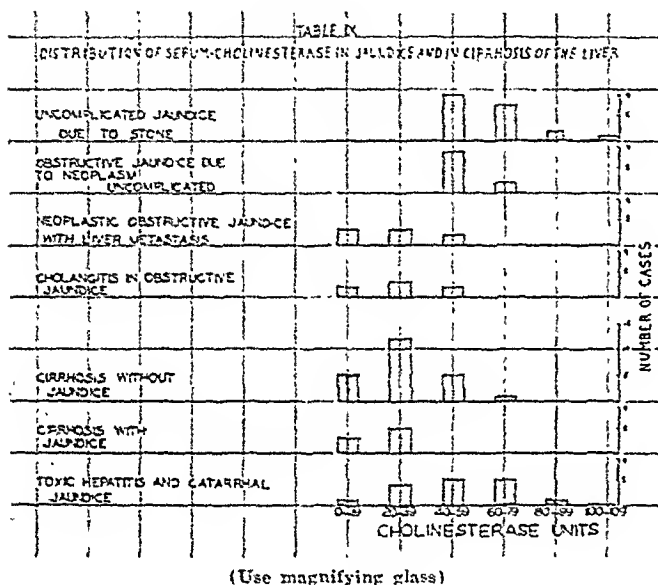
Distinction by cholinesterase values between obstructive and non-obstructive jaundice, if these categories be the sole grouping made, cannot be accurately made. Of 75 cases of jaundice 43 were obstructive and 32 non-obstructive. Of the obstructive cases 11 or about 25% were below 40; of 32 cases of non-obstructive jaundice 16 or 50% were below 40. However, the further segregation of these same cases into the groupings we have adopted, which are all recognized clinical-pathological entities, permit the clinically useful deductions summarized below. Additional information may be obtained with serial determinations.

## SUMMARY AND CONCLUSIONS

1. In cases of uncomplicated common duct stone with jaundice, serum cholinesterase values varied from 41 to 112; 21 of 25 observations were above 50; a value below 40 speaks strongly against this diagnosis.
2. In cases of neoplastic obstruction of biliary passages with jaundice but without cholangitis or metastases, cholinesterase values varied from 40 to 74; a value below 40 throws considerable doubt on this diagnosis.
3. In cases of obstructive jaundice with cholangitis or metastases, cholinesterase values varied from 6 to 58 with 13 of 17 observations below 40; a value above 60 points to the absence of these complications.
4. In the jaundice of "catarrhal icterus" or toxic hepatitis values for cholinesterase ranged from 28 to 100, 13 of 30 observations were below 50; 17 of 30 observations were above 50. Milder cases appeared to have higher values, and clinical improvement was accompanied by rise in the cholinesterase level.
5. In the most important clinical problem, the differential diagnosis between biliary tract obstruction and toxic hepatitis (including catarrhal jaundice) a high value is of no aid; a value below 40 speaks against obstruction provided metastases or cholangitis can be excluded.
6. Cases of cirrhosis of the liver, with or without jaundice, show low cholinesterase values, the range being 9 to 69; 36 observations were below 50, 32 of 38 below 40. A value above 40 speaks against cirrhosis; a value above 50 practically excludes cirrhosis.

## REFERENCES

1. Ammon, R. and Voss, G.: Die acetylcholinesterase-Wirkung des Blutes. *Pflügers Arch. für die gesamte Physiol.*, 235:393, 1935.
2. Antopol, W., Tuchman, L. and Schiffrin, A.: Choline Esterase Activity of Human Sera with Special Reference to Hyperthyroidism. *Proc. Soc. Biol. and Med.*, 36:46, 1937.
3. Antopol, W., Schiffrin, A. and Tuchman, L.: Decreased Choline Esterase Activity of Serum in Jaundice and in Biliary Disease. *Proc. Soc. Exp. Biol. and Med.*, 38:363, 1938.
4. McArdle, B.: The Serum Choline Esterase in Jaundice and Disease of the Liver. *Quart. J. of Med., New Series*, 9:107, 1940.
5. Milhorat, A. T.: The Choline Esterase Activity of the Blood Serum in Disease. *J. Clin. Invest.*, 17:649, 1938.
6. Jones, M. S. and Stadie, W. C.: The Choline Esterase Content of the Muscle of Myasthenia Gravis and of the Serum of Four Groups of Clinical Conditions. *Quart. J. Exp. Physiol.*, Vol. 29, p. 63, 1939.
7. McGeorge, M.: Choline Esterase Activity in Disease. *Lancet*, 1:69, 1937.
8. Butt, H., Comfort, M., Dry, T. and Osterberg, A.: Values for Acetylcholine Esterase in the Blood Serum of Normal Persons and Patients with Various Diseases. *J. Clin. and Lab. Med.*, 27:649, 1942.



nicious anemia, 2 cases of marked painless jaundice in cardiac decompensation, without clinical evidence of pulmonary infarct. 2 cases of jaundice in leukemia. The values ranged from 14 to 55.

## DISCUSSION

In evaluating the data herein reported, it must be borne in mind that many different conditions may alter the serum cholinesterase level, as we and others have pointed out (5, 6, 7, 8.) Among these are hyperthyroidism, severe anemia, extensive carcinomatosis, cachexia, infections such as sepsis, subacute bacterial endocarditis, the pneumonias and non-specific ulcerative colitis. The presence of any of these must be noted and taken into account in evaluating a figure for cholinesterase obtained in a case of jaundice or suspected cirrhosis. It should also be borne in mind that the normals present a fairly broad band. All interpretations must, therefore, be made with great caution. With these reservations serum cholinesterase values may be used as an additional source of infor-

## A Consideration of the Hepatico-Renal Syndrome\*

By

CHAS. GORDON HEYD, B.A., M.D., F.A.C.S., D.M.Sc.†  
NEW YORK, NEW YORK

**I**N October, 1922, I called attention to three clinical syndromes that sometimes intervened after operations upon the biliary tract (1.) It was thought that in some way these complications were caused directly or indirectly by hepatic insufficiency. The cause of death following surgical procedures (2, 3) is ordinarily readily determined and embraces the usual post-operative complications such as cardiac dilatation; hemorrhage, shock; gastric dilatation; embolism and pulmonary collapse. In the three syndromes referred to none of these conditions could be demonstrated as a cause of death. In 1931 (4) it seemed that some descriptive term would prove more adequate in presenting the subject and the opinion was expressed that "liver death" was a distinct clinical entity. There were three overlapping but relatively distinct groups:

Group I. Liver deaths associated with hyperpyrexia and coma. Death ensues in 18 to 36 hours.

In this group the patients had a comparatively simple gall bladder operation. They were usually obese and gave a history of chronic gall bladder disease. Following cholecystectomy the recovery from the anesthesia was slow, in fact the patient never did emerge from the anesthesia. In four to six hours after the return to the ward the patient was in a semi-comatose state that passed into stupor and coma, with a rapidly ascending temperature to 105-106° F.

Group II. In this group liver deaths were associated with a steadily diminishing jaundice and stupor and coma. The final clinical picture was similar to that of a "cholemic death" in cases of cirrhosis of the liver.

This group is essentially different in its clinical manifestation. The patients have had a chronic and severe type of biliary duct infection with obstructive jaundice and usually have had a cholecystectomy. At the second operation the obstruction has been relieved by drainage of the common duct and the post-operative condition of the patient has been fairly satisfactory. After a variable period of from one to seven days the patient develops stupor, oliguria and dies in coma with hyperpyrexia.

Group III. In this group liver deaths were associated with a secondary renal degeneration of severe degree.

Patients in this group lacked the hyperpyrexia and the stupor progressing into coma. The patients in this group have had a chronic, severe type of gall bladder and duct disease. After 48 hours there is a distinct vasomotor collapse, a continuous and increasing degree of oliguria, with a marked elevation of the non-protein nitrogen. Anuria finally dominates the clinical picture and leads to death. This third group

is described under the caption of hepatico-renal syndrome.

In a series of 557 unselected cases of cholecystitis representing all types of disease, including carcinoma, there were 39 deaths—a mortality of 7 per cent. Eight of these were so-called "liver deaths." This represents a mortality of 1.4 per cent of the total number of patients and 20 per cent of the ones who died (5.) Boyce, Veal and McPetridge (6) in an analysis of 100 consecutive deaths reported liver deaths in 23 patients which is approximately the same mortality.

The liver (7) in chronic states of infection and toxemia acts very much as does a Berkfield filter. In infectious disease of the external biliary apparatus the liver is obviously called upon to exercise both a detoxifying and a bacteriolytic function. The net result is a varying degree—both qualitative and quantitative—of liver damage. If it were not for the remarkable regenerative function of the liver few persons could survive for any length of time the continuous assault of the by-products of infection. In chronic invalidism due to biliary infection there comes a time when the function of immunity begins to fail, with the development of widespread symptoms. Cases of so-called liver death or cases with the hepatico-renal syndrome exhibit the same pathological process in both organs except that the changes in liver tissue always precede the manifestations in the kidney. If and when the patients die from hyperpyrexia and coma the liver shows degeneration of the parenchyma. When these patients survive long enough they show at post-mortem similar changes in the renal parenchyma.

There are three mechanisms for the production of liver injury in which the protective function of the liver is at a disadvantage. The by-products of abdominal infection carried through (1) the lymphatic system or (2) by way of the portal system; (3) or via the intra-hepatic biliary system may produce types of liver degeneration that are alien to its normal evolutionary physiology.

Many diverse histological changes may be observed in the liver sections. In general there is evidence of (1) an accumulation of the products of infection about the intralobular vein (the central vein) and associated with round cell infiltration and necrosis of adjacent liver cells; (2) an ascending biliary infection producing an intrahepatic cholangitis and with the formation of bile thrombi and necrosis of adjacent liver cells, with "bile laking." The liver cells undergoing necrosis are finally absorbed leaving in their place connective tissue trabeculae and resulting in chronic fibrous interstitial hepatitis.

In my earlier experience the type of mortality which I am discussing was confined entirely to persons who were operated upon for disease of the gall bladder or biliary tract, and the phrase "liver deaths" was coined to express this concept. It was apparent that other

\*Presented before the Chicago Medical Society, Chicago, Ill., February 18, 1942.

†Submitted April 15, 1942.

†Professor of Surgery, New York Post-Graduate Medical School, Columbia University.

operative procedures occasioned this type of mortality and it has been demonstrated that almost any type of surgical intervention, in certain individuals, may initiate a toxemic process leading to death and which parallels the first description of so-called liver deaths. It was therefore of great interest to learn of well documented cases of liver death occurring in persons as the result of a crushing injury to the liver and not as a complication of a surgical operation. One of the first cases described was that of a young woman who was injured in an automobile accident and died with hyperpyrexia and coma (8.) Other cases (9, 10) were reported with the same history of a crushing injury to the liver, with death in 18 hours with hyperpyrexia and coma. Some of these cases were presented with post-mortem studies and in every instance the necrosis of the liver was associated with necrosis of the cortex of both kidneys. The sequence of destruction of liver tissue, with secondary necrosis of the tubules of the kidney led to the concept of a primary liver defect and a secondary renal injury and hence the name of the "hepatico-renal syndrome."

In group I the patients who died in 18 to 24 hours with hyperpyrexia and coma died from an overwhelming toxemia and did not live long enough to develop what I believe to be the inevitable secondary renal changes. The patients in the other two groups were able to sustain life for a longer period than group I with the result that autopsy invariably showed the changes in the renal tubules. While the evidence presented up to date has been largely clinical, with very few positive post-mortem findings, the occurrence of the condition has been certified by many competent observers and it is of interest that some of the surgeons who first denied its existence and stated they had never had cases in their own experience later recanted and published cases that were exactly similar to those first described.

Boyce (11, 12) was able to produce a similar syndrome in experimental animals by injecting into dogs saline and alcoholic extracts from "the livers of patients who died hyperpyrexia deaths after biliary surgery." Dogs were injected intraperitoneally with each extract. At autopsy the dogs receiving the alcoholic extractions of liver tissue showed no significant changes but the dogs injected with the liver extract prepared with saline solution and water showed parenchymatous degeneration of liver cells with similar changes in the convoluted tubules of the kidney.

Some clinical evidence supports my view and is supplied by a study of the post-operative course of a number of patients who had had some symptoms of the hepatico-renal syndrome but survived. There is a certain feature common to all of these cases and that

is the presence of an operative wound containing a considerable amount of tissue serum. This material must be absorbed and metabolized by the liver. The absorption is characterized clinically by fever, lethargy verging on stupor, beginning oliguria and a rise in the nonprotein nitrogen of the blood. After varying periods recovery ensues. It is suggested that the toxin present in these conditions and which is the lethal agent in liver deaths is an incompletely metabolized protein derivative.

Closely related to this problem is that of water and chemical balance. "The ability of the liver to hold widely varying quantities of fat is one of the most characteristic of this organ." "Any considerable increase in the fat content of the liver, even an increase produced by physiologic means, impairs the organ in regard to some of its other functions" (13.) After long continued dietary restrictions or chronic illness there is an insufficient amount of protein in the liver. The giving of a high protein, high carbohydrate and low fat diet is the most effective way to reduce lipid concentration in the liver and gain the maximum liver protection in the preparation of patients for operation on the biliary tract (14.)

There is also a curious and yet unexplained relationship to the effect of Vitamin K. Not only does the administration of Vitamin K before operation remove the high incidence of operative and post-operative bleeding in the patient with jaundice, but it is our opinion that deficiency of the Vitamin K status in patients interferes with the entire chemistry of liver function. The giving of an adequate dose of Vitamin K before operation not only prevents bleeding but it helps the functions of the liver.

Draining the fossa of the gall bladder following cholecystectomy not only provides an exit for bile that may have leaked but it serves the important function of preventing the accumulation of tissue fluids. The clinical course of patients in my group II is such as to impress the clinician that if obstructive jaundice is continued long enough the mere relief of the obstruction will not prevent death. Experiments by Boyce and McFetridge (15) on the sudden decompression of the biliary system in complete obstructive jaundice are very illuminating.

Long continued external biliary obstruction is associated with a severe edema of the liver (16.) Edema of the liver creates a vicious circle and inhibits liver function and diminishes "liver protection." As long as this edematous fluid is fixed in the liver by the continuation of the obstruction it probably is neither absorbed or metabolized but a sudden decompression by the removal of the obstruction mobilizes this contained liver fluid and it in turn is capable of producing widespread toxemia.

## REFERENCES

1. Heyd, Chas. Gordon: Hepatitis Associated with or Sequential to Inflammatory Diseases of the Abdomen. *Long Island Med. J.*, Jan., 1923.
2. Heyd, Chas. Gordon: Hepatitis, an Associated Condition with Gall Bladder Disease. *Transactions of the Twenty-sixth Annual Meeting of the American Gastro-Enterological Association*, April, 1923.
3. Heyd, Chas. Gordon: The Liver and Its Relation to Chronic Abdominal Infection. *Ann. Surg.*, Jan., 1924.
4. Heyd, Chas. Gordon: "Liver Deaths" in Surgery of the Gall Bladder. *J. A. M. A.*, Vol. 97, Dec. 19, 1931.
5. Heyd, Chas. Gordon: Complications of Gall Bladder Surgery. *Ann. Surg.*, Jan., 1937.
6. Boyce, F. F., Veal, J. R. and McFetridge, E. M.: Analysis of Mortality of Gall Bladder Surgery, with Special Note on So-called Liver Death. Based on 400 Consecutive Surgical Cases and 100 Consecutive Surgical Deaths in New Orleans Charity Hospital. *S. G. O.*, 63, July, 1936.
7. Heyd, Chas. Gordon, Killian, John A. and MacNeal, Ward J.: The Liver and Its Relation to Chronic Abdominal Infection. *Beaumont Foundation Lecture*, C. V. Mosby, 1924.
8. Furtwaengler, A.: Diffuse Rindennekrose beider Nieren nach Leberruptur (Ein Beitrag zu den angio-pastischen Krankheitsbildern in der Chirurgie.) *Krankheitsforschung*, 4:349-374, June, 1927.

9. Orr, T. C. and Helwig, F. C.: Liver Trauma and the Hepatorenal Syndrome. *Ann. Surg.*, Oct., 1939.
10. Stanton, E. MacD.: Immediate Causes of Death Following Operations on Gall Bladder and Ducts. *Am. J. Surg.*, May, 1930.
11. Boyce, Frederick F.: An Experimental Study of the So-called Liver Death Syndrome in Biliary Surgery. *Proceedings of the Society for Experimental Biology and Medicine*, 32:479-481, 1934.
12. Boyce, Frederick F.: The Role of the Liver in Surgery. Pub.: Charles C. Thomas, Baltimore, Md., 1941.
13. Mann, Frank C.: The Liver and Medical Progress. *J. A. M. A.*, Vol. 117, No. 19, Nov. 8, 1941.
14. Sparing the Liver. Editorial: *J. A. M. A.*, Vol. 117, No. 21, 1786:1787, Nov. 22, 1941.
15. Boyce, F. F. and McFetridge, E. M.: The So-called "Liver Death": An Experimental Study of Changes in the Biliary Ducts Following Decompression of the Obstructed Biliary Tree. *Arch. Surg.*, 32:1030-1986, June, 1936.
16. Heyd, Chas. Gordon: The Liver and Gall Bladder Disease. *New York State Journal of Medicine*, Vol. 35, No. 13, July 1, 1936.

## II. Intestinal Absorption of an Amino-Acid Mixture in Patients With Chronic Idiopathic Ulcerative Colitis and Entero-Colitis

By

L. ZETZEL, M.D., B. M. BANKS, M.D.

and

E. SAGALL, M.D.

BOSTON, MASSACHUSETTS

IN a previous communication (1), a method was described for estimating the rate of absorption of a mixture of amino acids\* from a closed jejunal loop in normal individuals. The method utilized a modification of the Miller-Abbott tube for rapid intestinal intubation (2) and consisted essentially of the introduction of a 10 per cent solution of an enzymatic hydrolysate of casein into a 60 cm. closed loop of upper jejunum, each end of which was occluded by an inflated balloon. At the end of 30 minutes, the contents of the loop were removed by suction, after which the loop was washed four times with 100 cc. of water during the next 30 minutes. The total amount recovered consisted of unabsorbed hydrolysate mixture and intestinal juices. As a result of these observations, it was found that approximately 85 per cent of the total nitrogen and the tyrosine component originally introduced was absorbed from such isolated loops in normal subjects. At that time it was stated that this technique, while laborious and not adapted to precise interpretation in terms of grams absorbed per unit area, yielded fairly constant results and could serve as a basis of comparison with similar studies in patients with various pathological conditions.

The present report deals with the absorption of this amino-acid mixture in three patients with chronic idiopathic ulcerative colitis and two patients with chronic entero-colitis. All patients were studied during an exacerbation of their disease which had produced, in some cases, signs of marked Vitamin B deficiency consisting of glossitis, peripheral neuritis and cheilosis.

### RESULTS

Four of the five patients showed impaired absorption of the amino-acid mixture, only 43 to 64 per cent of the total nitrogen, and 49 to 60 per cent of the tyrosine component introduced into the closed loop being absorbed. This is in contrast to the observations made in the remaining patient with chronic ulcerative colitis who yielded values for the absorption of the mixture which were within normal limits. It is of interest that this patient, Case 3, although having defi-

nite chronic disease involving the entire colon, showed no clinical evidence of Vitamin B deficiency, and his general state of nutrition was much better than that of the other patients studied. One patient, Case 5A, was studied early in the course of the disease, when there was no roentgenological evidence of involvement of the intestinal tract, although symptoms of bloody diarrhea and abdominal cramps were present, and glossitis and cheilosis had already developed. At this time her absorptive capacity for the amino-acid mixture was normal. One year later, as the disease progressed and the diarrhea became more severe, the terminal ileum and colon showed roentgenological evidence of an ulcerative process, and there was definite impairment of absorption, only 61 per cent of the test mixture being absorbed, Case 5B.

### DISCUSSION

The possible mechanisms involved in the production of deficiency states in patients with ulcerative colitis and entero-colitis include those of anorexia, increased gastro-intestinal motility, loss of essential foods and minerals as a consequence of hemorrhage and exudation (3) and impaired absorptive capacity of the upper intestinal tract. The validity and relative importance of the first three factors can readily be determined and verified. However, the interpretation of impaired absorptive capacity in the small intestine is complicated by the fact that such impairment of function may be due either to the disease itself or to the associated Vitamin B deficiency. In experimental Vitamin B deficiency in animals, impaired absorption due to deranged intestinal function has been noted by Pierce, Osgood and Polansky (4), McCarrison (5, 6) and Gross (7); these authors suggested that similar impairment of gastro-intestinal function might occur in patients with Vitamin B deficiency. Mackie and Pound (8) noted evidence of vitamin deficiency in a large percentage of patients with chronic ulcerative colitis and found abnormalities in the roentgen appearance of the small intestine when the deficiency state was clinically marked. These findings were coarse mucosal markings, variation in contour and size of the lumen with segmented distribution of barium in dilated and isolated coils. The similarity of these changes to those observed in sprue suggests that in

From the Medical Research Department, Beth Israel Hospital, and the Department of Medicine, Harvard Medical School, Boston, Mass.

\*This was supplied through the courtesy of Mead, Johnson and Company.

Submitted April 6, 1942.

both diseases impaired function of the small intestine contributes to the deficiency state.

Direct measurement of the absorptive capacity of the gastro-intestinal tract in man are few. Heath and Fullerton (9) used the appearance time of iodine in the saliva after its oral administration as a test of such capacity. Beams, Free and Glenn (10) measured the absorption of galactose from the gastro-intestinal tract as reflected in rises in blood level in patients with non-tropical sprue, pernicious anemia and pellagra. Groen (11), also utilizing a modification of the Miller-Abbott tube, found diminished absorption of glucose from the upper gastro-intestinal tract of patients with a variety of diseases, including one instance of chronic ulcerative colitis. The studies of Groen in this one patient are the only ones which have yielded data bearing directly on the problem of gastro-intestinal absorption in chronic ulcerative colitis, where the continuity of the intestinal tract is maintained intact. The present study indicates directly that patients with chronic idiopathic ulcerative colitis or enterocolitis with clinical evidence of severe malnutrition and deficiency disease are unable to absorb an amino-acid mixture from the upper jejunum to a

digestion due to incomplete splitting of ingested protein. However, our experiments prove that a significant degree of malabsorption occurs, since the material used in our studies was an enzymatic hydrolysate of casein in which at least 80 per cent of the nitrogen already existed in the form of amino acids. Nevertheless, the possibility that incomplete digestion also occurs in the small intestine of patients with chronic ulcerative colitis or enterocolitis cannot be excluded. The results of the present study and those of Elsom et al (12) in patients with ileostomies afford strong evidence bearing directly on the role played by small intestinal dysfunction in contributing to the development of the deficiency state seen in severe ulcerative colitis. The derangement of absorption undoubtedly contributes to the clinical manifestations by perpetuating a vicious cycle in spite of an adequate oral intake. Parenteral administration of essential and accessory food factors is therefore clearly indicated.

The mechanism of this impaired intestinal absorption may be attributed directly to an associated Vitamin B deficiency as Mackie and Mills (13) suggest in interpreting the roentgenological abnormalities seen so commonly in the small intestine of patients with severe and chronic ulcerative colitis. However, this assumption is not borne out by a study of our case reports. In one case, there was marked malabsorption long before clinical evidence of Vitamin B deficiency appeared. In another case, in spite of glossitis and cheilosis already visible in the course of terminal ileitis with colitis, normal values were obtained for intestinal absorption of the test mixture.

It should be noted that the method of the present study tests only the absorptive capacity of approximately 60 cm. of upper jejunum in one hour's time. Early in the course of the disease, with the entire small intestine available for absorption, slight impairment might not be important. With progression of the disease, however, there is encroachment on the reserve absorptive capacity of the bowel to compensate for essential elements lost in rectal discharges. Such diminution of function then becomes more severe and clinically more significant.

### CONCLUSIONS

1. Absorption of an enzymatic hydrolysate of casein from closed upper jejunal loops was studied in five patients with severe and chronic idiopathic ulcerative colitis or enterocolitis.

2. In four patients there was marked impairment of absorption as compared with normal individuals. In the remaining patient, whose general nutrition was well maintained in spite of chronic disease of the large bowel, small intestinal absorption, as determined by the test mixture used, was found to be normal.

3. The nature and mechanism of this dysfunction of the small intestine is discussed, and its significance in contributing to the picture of a deficiency state is emphasized.

4. Such a defect in small intestinal function, when added to the well established gross involvement of the colon and terminal ileum, enlarges our concept of chronic idiopathic ulcerative colitis and ileocolitis to a disorder embracing the entire intestinal tract.

TABLE I

| Case No. | Nitrogen*       |               |            | Tyrosine**      |               |            |
|----------|-----------------|---------------|------------|-----------------|---------------|------------|
|          | Mgm. Introduced | Mgm. Absorbed | % Absorbed | Mgm. Introduced | Mgm. Absorbed | % Absorbed |
| 1        | 1170            | 505           | 43         | 284             | 141           | 50         |
| 2        | 1170            | 608           | 53         | 284             | 141           | 50         |
| 3        | 1170            | 996           | 85         | 284             | 215           | 76         |
| 4        | 1170            | 750           | 64         | —               | —             | —          |
| 5A       | 1170            | 969           | 83         | 284             | 209           | 71         |
| 5B       | 1170            | 715           | 61         | 284             | 176           | 62         |

\*Normal Nitrogen Absorption—85%.

\*\*Normal Tyrosine Absorption—86%.

degree comparable with normal individuals. That this degree of impairment in absorption is correlated with the severity of the clinical evidence of malnutrition is suggested by a study of the case reports. However, it is probably not of etiological significance in initiating the disease, since the one patient with chronic ulcerative colitis whose general state of nutrition was well maintained, in spite of chronic disease in the colon over a period of several years, disclosed normal results for intestinal absorption by the test employed in this study.

Elsom, Dickey and Chornock (12) have recently published data on the nitrogen balance in several patients with idiopathic ulcerative colitis in whom ileostomy had previously been performed. They found an abnormally large amount of nitrogen excreted through the ileostomy in four of seven cases. The factor of increased intestinal motility was not present in their patients with ileostomy. Elsom and his co-workers raise the question as to the nature of the defect in small intestinal function, since their data do not differentiate between impaired absorption of normally broken down nitrogenous products and faulty



## REFERENCES

1. Zetzel, L. and Banks, B. M.: I. Intestinal Absorption of an Amino-Acid Mixture in Normal Subjects. *Am. J. Dig. Dis.*, 8:21, 1941.
2. Miller, T. G. and Abbott, W. O.: Intestinal Intubation. A Practical Technique. *Am. J. Med. Sci.*, 187:595, 1934.
3. Welch, C. S., Wakefield, E. G. and Adams, M.: Metabolic Studies on Chronic Ulcerative Colitis. *J. Clin. Invest.*, 16:161, 1937.
4. Pierce, H. B., Osgood, H. S. and Polansky, J. B.: The Absorption of Glucose from the Alimentary Tract of Rats Deprived of Vitamin B Complex. *J. Nutrition*, 1:247, 1929.
5. McCarrison, R.: The Pathogenesis of Deficiency Disease. *Ind. J. Med.*, 7:167, 1919.
6. McCarrison, R.: The Pathogenesis of Deficiency Disease. *Ibid.*, 7:283, 1919.
7. Gross, L.: Effect of Vitamin Deficient Diets on Rats. *J. Path. and Bact.*, 27:27, 1924.
8. Mackie, T. T. and Pound, R. E.: Changes in the Gastro-Intestinal Tract in Deficiency States with Special Reference to the Small Intestine. *J. A. M. A.*, 104:613, 1935.
9. Heath, C. W. and Fullerton, H. W.: The Rate of Absorption of Iodide and Glycine from the Gastro-Intestinal Tract in Normal Persons and in Disease Conditions. *J. Clin. Invest.*, 14:475, 1935.
10. Beams, A. J., Free, A. H. and Glenn, P. M.: The Absorption of Galactose from the Gastro-Intestinal Tract in Deficiency Disease. *Am. J. Dig. Dis.*, 8:415, 1941.
11. Groen, J.: The Absorption of Glucose from the Small Intestine in Deficiency Disease. *New Eng. J. Med.*, 218:247, 1938.
12. Elsom, K. A., Dickey, F. G. and Chornock, F. W.: Functional Disturbance of the Small Intestine in Chronic Idiopathic Ulcerative Colitis. *Am. J. Dig. Dis.*, 9:74, 1942.
13. Mackie, T. T. and Mills, M. A.: Changes in the Small Intestine Associated with Deficiency Disease. *Am. J. Dig. Dis.*, 7:480, 1940.

## The Effect of Histamine on Cinchophen Ulcers Produced in Dogs

By

B. SLUTZKY, M.D.

and

N. DIETZ, Ph.D.

OMAHA, NEBRASKA

with technical assistance of

M. E. STONER, M.S.

and

B. J. O'LOUGHLIN, M.S.

**R**ESearch investigations and clinical reports concerning the use of histaminase as a therapeutic agent have been controversial in nature ever since Best and McHenry (1) isolated the substance in 1930. Roth and Horton (2) have summarized its physiological effects as well as its therapeutic value in cold allergy, histaminic cephalalgia, serum sickness, insulin allergy, urticaria, and vasomotor rhinitis.

There appears to be contradictory evidence concerning the inhibitory effect of histaminase on gastric acidity. Horton (3) in 1932 reported the histamine like effect on gastric acidity in cases of cold allergy. In 1936 he and his coworkers (4) reported further studies on such cases and stated that cold allergy was amenable to treatment with histamine. One year later Roth and Horton (5) presented a case where gastric acidity was measured before and after administration of histaminase and found that there was a marked decrease in rise of gastric acidity in the second test. Such changes were later noted in normal subjects; namely, a rise in gastric acidity when patient was immersed in a cold bath, and a decrease in gastric acidity when histaminase was previously administered. The same inhibitory effect was reported when histaminase was administered before the injection of histamine.

The inhibitory effect of histaminase on gastric secretion has not received confirmation from other investigators. Atkinson, Ivy and Bass (6) administered large doses of histaminase to human subjects and dogs. They found no significant decrease of gastric secretory response when this was followed by injection of histamine. Likewise, Necheles and Olson (7) conclude from their experiments that histaminase has no depressant effects on salivary, gastric, biliary, or

pancreatic secretions of dogs stimulated by histamine. Best and McHenry (8) stated rather pointedly that from their investigations there was no physiological basis for the clinical use of histaminase.

However, the clinical application of the apparent inhibitory action of histaminase on gastric acidity has been used by some physicians in the treatment of peptic ulcer (9, 10.) These reports of clinical improvement of cases of peptic ulcer are given without definite evidence of studies in decrease of acid secretions. It is well known by clinicians that cases of peptic ulcer may respond to various unorthodox types of therapy (11.)

Our experiment was to study the effect of histaminase on peptic ulcers in dogs produced by the administration of cinchophen. Our previous study on effects of Antuitrin-S and Posterior pituitary extract on cinchophen ulcers (12) was to serve as a basis of comparison as to the effectiveness of treatment with histaminase. It was then reported that the average survival period was 29 days—the animals dying usually of perforated ulcer.

Method: The dogs were fed on a regular kennel diet. Animals that were studied for secretory curves were given Purina dog biscuits. Each dog received approximately two grams of cinchophen daily except Sunday. Histaminase (Torantil) 8-12 units daily was injected intramuscularly. The dosage varied with the supply of the drug on hand.

(Note: We are indebted to the Winthrop Chemical Company for the generous supply of Torantil.)

### COMMENT

A study of our results shows that practically all the dogs developed typical peptic ulcers that are found after the administration of cinchophen despite the continuous use of histaminase. It may be stated that during the study we received some batches of the Torantil which were of doubtful potency possibly

affecting five animals (No. 298, 538, 539, 550 and 537.) Nevertheless, the results were almost uniformly the same in all the animals—formation of peptic ulcer.

Examination of acid secretions in several animals by the Wilhelmsj-O'Brien technique (13) when histaminase, cinchophen and a combination of both were given to the animals revealed no definite inhibition of acid secretions. The curves did not differ from those noted after normal gastric stimulation. (Chart I)

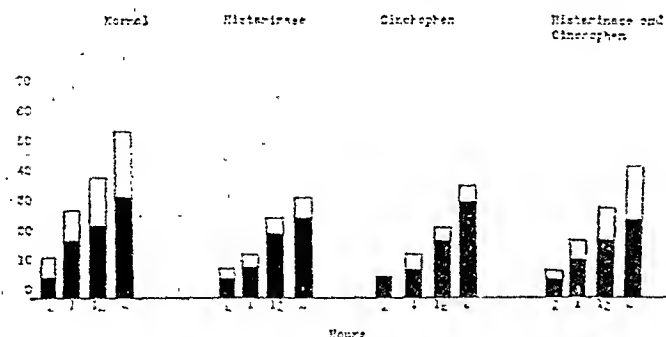


Chart I. Height of rectangles shows total amount of fluid secretions entering stomach per 100 cc. of gastric contents. The *Black* portion indicates the fluid of the acid secretion and the *White* portion the fluid of the non-acid secretions. The scale increasing by 10 represents the fluid of secretions per 100 cc. of gastric contents. These secretory curves are representative of the many studied on this previously standardized dog, as well as other animals.

The average survival period of the animal is prolonged in comparison to our results in treating cinchophen dogs with Antuitrin-S and with Posterior Pituitary Extract, 52 days and 29 days respectively. Some animals survived for an unusually long period tending to raise the average survival time. Yet it may be significant that the ulcerative process was not prevented in these animals such as is possible by well recognized methods of therapy (14.)

### SUMMARY

There is no definite confirmation by reliable investigators concerning the inhibitory action of histaminase on gastric acidity as expressed by Roth, et al.

The average survival period of dogs treated with

histaminase is increased in comparison to dogs treated with Antuitrin-S and with Posterior Pituitary Extract. However, histaminase did not prevent the development of peptic ulcers in the dogs fed with cinchophen.

Experimental data seem to demonstrate that histaminase is of no value in the treatment or prevention of peptic ulcer in the dog.

TABLE I

| Dog | Total Days Treated | Total Dose of Cinchophen | Total Dose of Histaminase | Weight of Dog |                                       |
|-----|--------------------|--------------------------|---------------------------|---------------|---------------------------------------|
| 394 | 212                | 424                      | 1391                      | 30 lbs.       | Perforated ulcer                      |
| 448 | 43                 | 86                       | 468                       | 30            | Chronic ulcer and erosions            |
| 505 | 81                 | 162                      | 293                       | 25            | Several ulcers—peritonitis            |
| 510 | 24                 | 48                       | 144                       | 27            | Shallow ulcer—died of distemper       |
| 511 | 88                 | 176                      | 1623                      | 26            | Two perforated ulcers—peritonitis     |
| 512 | 28                 | 56                       | 168                       | 16            | Two deep ulcers                       |
| 523 | 27                 | 54                       | 162                       | 23            | Ulceration—hemorrhage                 |
| 532 | 46                 | 92                       | 190                       | 16            | Large perforated ulcer                |
| 531 | 51                 | 102                      | 547                       | 39            | Perforated ulcer                      |
| 298 | 27                 | 54                       | 168                       | 24            | Multiple small ulcerations—hemorrhage |
| 538 | 17                 | 34                       | 162                       | 13            | Perforated ulcer                      |
| 539 | 24                 | 48                       | 218                       | 13            | Perforated ulcer                      |
| 550 | 25                 | 50                       | 273                       | 22.5          | Perforated ulcer                      |
| 537 | 23                 | 46                       | 212                       | 14            | Perforated ulcer                      |
| 419 | 77                 | 154                      | 1058                      | 26.5          | Perforated ulcer                      |
| 596 | 72                 | 144                      | 1012                      | 17            | Shallow hemorrhagic ulceration        |
| 522 | 29                 | 58                       | 367                       | 20            | Several deep ulcers                   |
| 567 | 17                 | 34                       | 209                       | 18            | Large perforated ulcer                |
| 542 | 63                 | 126                      | 889                       | 23.5          | Large perforated ulcer                |
| 558 | 63                 | 126                      | 889                       | 26.5          | Chronic ulcer—intussusception         |
| 559 | 34                 | 68                       | 454                       | 16            | Perforated ulcer                      |

Average Survival: 52 days.

### REFERENCES

- Best, C. H. and McHenry, E. W.: The Inactivation of Histamine. *J. Physiol.*, 70:349, 1930.
- Roth, Grace M. and Horton, B. T.: Histaminase, Physiologic Effect on Man and Its Therapeutic Value in Medicine. *Bulletin of New York Academy of Medicine*, 16:570-582, 1940.
- Horton, B. T. and Brown, G. E.: Histamine-like Effects on Gastric Acidity Due to Cold. *Proc. Staff Meet., Mayo Clinic*, 7:367-371, 1932.
- Horton, B. T., Brown, G. E. and Roth, Grace M.: Hypersensitivity to Cold with Local and Systemic Manifestations of a Histamine-like Character; Its Amenability to Treatment. *J. A. M. A.*, 107:1263-1268, 1936.
- Roth, Grace M. and Horton, B. T.: Hypersensitivity to Cold; Treatment with Histamine and Histaminase. Report of Case. *Proc. Staff Meet., Mayo Clinic*, 12:129-133, 1937.
- Atkinson, A. J., Ivy, A. C. and Bass, Vivian: The Effect of Histaminase on the Gastric Secretory Response to Histamine. *Am. J. Physiol.*, 132:51-56, 1941.
- Neches, H. and Olson, Wm. H.: Histaminase: An Experimental Study. *Am. J. Dig. Dis.*, 8:217-219, 1941.
- Best, C. H. and McHenry, E. W.: A Note on Histaminase. *The Canadian Med. Ass'n J.*, 43:163-164, Aug., 1940.
- Nakoda, J. R.: The Treatment of Duodenal Ulcer with Histaminase. *Rev. of Gastroenterol.*, 6:389-394, 1939.
- O'Halloran, P.: Histaminase in the Treatment of Peptic Ulcer. *Northwest Medicine*, 39:216-217, 1940.
- Sandweiss, D. J.: Comparative Results with Dietetic, Parenteral and Surgical Treatment in Peptic Ulcer. *J. A. M. A.*, 105:700-707, Feb. 27, 1937.
- Slutzky, B., Wilhelmsj, C. M. and Stoner, M.: The Effect of Antuitrin-S and Posterior Pituitary Extract on Cinchophen Ulcers in Dogs. *Am. J. Dig. Dis.*, 8:469-470, Dec., 1941.
- Wilhelmsj, C. M., O'Brien, F. T. and Hill, F. C.: An Improved Gastric Test Meal. *Am. J. Dig. Dis.*, 3:319-325, 1935-1937.
- Stalker, L. K., Bollman, J. L. and Mann, F. C.: Prophylactic Treatment of Peptic Ulcer Produced Experimentally with Cinchophen. *Am. J. Dig. Dis.*, 3:822-827, 1936-1937.

# Clinical Studies of Amino Acids

## I. The Effect of Oral Administration of a Solution of an Amino Acids Mixture on Gastric Acidity\*

By

JEROME S. LEVY, M.D.

and

KENNETH A. SILER, Ph.D.†

LITTLE ROCK, ARKANSAS

**R**ECENT studies of a mixture containing all the essential amino acids in solution have focused attention on the therapeutic possibilities of such a mixture. Elman and Weiner (1) and Elman (2) have reported the maintenance of a positive nitrogen balance by the parenteral administration of an amino acids mixture. The preparation used was a "purified casein digest prepared with pancreatic enzymes." The use of this preparation has opened a new avenue of approach to the treatment of gastro-intestinal disorders, including bleeding peptic ulcers. There has been a widespread discussion of the relative merits of the full feeding plan in the therapy of these bleeding ulcers as contrasted to a starvation or semi-starvation regimen. The proponents of the former explain the lowered mortality on the basis of the improved nutritional state of their patients, whereas the advocates of the latter plans base their arguments on the lessened stimulus to motor and secretory activity. The possibility of combining the advantages of both of the above plans has suggested an investigation of the gastric response to the oral administration of a solution of an amino acids mixture.

### METHOD

Forty-eight students who volunteered as subjects for these experiments were divided into two groups. Thirty students were given a solution of the amino acids of hydrolyzed casein (amigen)‡, which had been adjusted to a pH of 6.6 with sodium hydroxide. Eighteen students were given a solution of amigen, which had not been so adjusted and whose pH was 4.5. In each instance, a Rehfuß tube was passed into the fasting stomach, the fasting contents withdrawn, and the test meal (300 cc. of a 10% solution of the amino acids preparation) introduced through the tube. Specimens were withdrawn at ten minute intervals until less than twenty cc. could be obtained or to the end of a ninety minute period. The test specimens were titrated in the usual manner against N/10 sodium hydroxide, using Toepfer's reagent and phenolphthalein as indicators. The color of the amino acids mixture made the end point somewhat difficult to detect but this was corrected by diluting the specimen with distilled water before titration. To maintain uniformity the same dilutions were made in all specimens

even though some were lighter in color than others. The pH of all specimens of the second group was determined by glass electrode potentiometer. (Leeds and Northrup—Universal pH meter No. 7661.)

### RESULTS

*Free Acidity*—There is a uniform absence of free acidity in those samples taken at ten and twenty minutes after the instillation of the test meal of

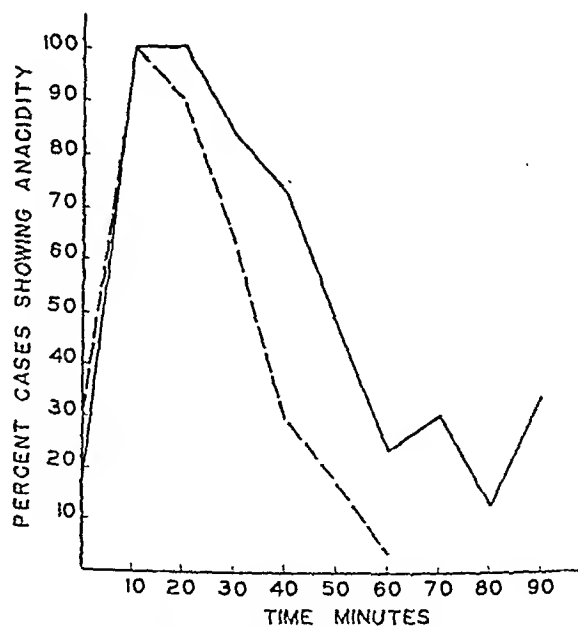


Fig. 1. Per cent of cases exhibiting no free acid at successive ten minute intervals.—Data from Group I, Table I.—Data from Group II, Table I. The curve extending beyond 60 minutes has progressively less significance because of reduced number of cases.

amigen. In the first group of 30 students (who were given the solution to which sodium hydroxide had been added), free acid was absent in all specimens at the ten minute interval. At thirty minutes free acid was still absent in all specimens from the second group of 18 students (who had been given the amigen without the addition of NaOH.) Twenty-seven of the first thirty students had an absence of free acid at this same interval making a total of 45 out of the 48 in whom there was no free acid for twenty minutes. It is evident (Fig. 1) that the rate of appearance of free acid increases rapidly after thirty to forty minutes.

\*Research paper No. 526, Journal series, University of Arkansas.

†From the Department of Medicine and the Department of Physiology and Pharmacology, University of Arkansas, School of Medicine, Little Rock, Arkansas.

‡Amigen is a purified enzymatic hydrolysate of casein prepared by the action of pork pancreas on a high grade of acid precipitated casein. The materials used were generously supplied by Mead, Johnson and Company, Evansville, Indiana.

Submitted April 1, 1942.

TABLE I

| Group No. 1   |         | TEST ACID  |         |         |         |         |         |         |                 |
|---------------|---------|------------|---------|---------|---------|---------|---------|---------|-----------------|
|               | Fasting | 10 min.    | 20 min. | 30 min. | 40 min. | 50 min. | 60 min. | 70 min. |                 |
| Average       | 21.1    | 0          | 1.47    | 13.5    | 33.9    | 52.0    | 60      | 70      |                 |
| Extremes      | 0-62    | 0          | 0-16    | 0-70    | 0-96    | 0-110   | 0-106   | -70     |                 |
| No. of Cases  | 30      | 30         | 30      | 30      | 30      | 29      | 25      | 1       |                 |
| Group No. 2 - |         |            |         |         |         |         |         |         |                 |
|               | Fasting | 10 min.    | 20 min. | 30 min. | 40 min. | 50 min. | 60 min. | 70 min. | 80 min. 90 min. |
| Average       | 20.7    | 0          | 0       | 3.2     | 8.2     | 15.1    | 24.2    | 30.5    | 35.8 38.3       |
| Extremes      | 0-70    | 0          | 0       | 0-40    | 0-60    | 0-40    | 0-80    | 0-70    | 0-70 0-85       |
| No. of Cases  | 18      | 18         | 18      | 18      | 18      | 15      | 13      | 10      | 8 3             |
| Group No. 1   |         | TOTAL ACID |         |         |         |         |         |         |                 |
|               | Fasting | 10 min.    | 20 min. | 30 min. | 40 min. | 50 min. | 60 min. | 70 min. |                 |
| Average       | 31.8    | 61.1       | 72.1    | 77.3    | 83.9    | 86.2    | 89.2    | 94      |                 |
| Extremes      | 4-105   | 40-132     | 38-120  | 52-106  | 52-154  | 52-130  | 46-138  | -94     |                 |
| No. of Cases  | 30      | 30         | 30      | 30      | 30      | 29      | 26      | 1       |                 |
| Group No. 2 - |         |            |         |         |         |         |         |         |                 |
|               | Fasting | 10 min.    | 20 min. | 30 min. | 40 min. | 50 min. | 60 min. | 70 min. | 80 min. 90 min. |
| Average       | 70.2    | 101.9      | 95.2    | 96      | 85.6    | 91.1    | 85.5    | 80.5    | 81.1 87         |
| Extremes      | 1-80    | 20-191     | 40-150  | 18-150  | 10-132  | 20-143  | 28-135  | 12-118  | 17-131 55-106   |
| No. of Cases  | 15      | 18         | 18      | 18      | 18      | 15      | 13      | 10      | 8 3             |

The percentages shown in Fig. 1 after sixty minutes are of questionable value because of the reduced number of individuals from whom samples could be obtained. (These are included in Table I.)

**Total Acidity**—The values of total acidity varied widely (Table I.) There is an apparent tendency for these values to reach a higher level than with the usual test meal, which cannot be anticipated on the basis of the free acid present in the specimen. There was a greater variation in the extremes of total acidity

specimen had a pH below 3.5. That the buffering action of the amigen solution is sustained is shown by the fact that a total of thirteen specimens still showed a pH of 3.5 or higher at fifty minutes.

## COMMENT

The role of native proteins and amino acids in the buffering systems of the body is well known. A solution of amino acids introduced into the stomach has been shown to buffer adequately the acid gastric contents and to maintain an intragastric pH of 3.5 or better for a significant interval of time.

At pH 3.5, the usual end point of titration when Toepfer's reagent is used, the ionization of hydro-

TABLE II

Number of specimens in each pH range, for consecutive 10 minute periods, following ingestion of 300 cc. of 10% amigen solution

|            | pH Range |         |         |           |       |
|------------|----------|---------|---------|-----------|-------|
|            | 4.5+     | 4.0-4.5 | 3.5-4.0 | Below 3.5 | Total |
| Fasting    | 3        | 0       | 0       | 15        | 18    |
| 10 Minutes | 10       | 8       | 0       | 0         | 18    |
| 20         | 7        | 11      | 0       | 0         | 18    |
| 30         | 3        | 9       | 5       | 1         | 18    |
| 40         | 5        | 4       | 6       | 3         | 18    |
| 50         | 2        | 4       | 7       | 2         | 15    |
| 60         | 1        | 2       | 3       | 7         | 13    |

when the pH of the test meal was not adjusted with NaOH and the mean values were higher for the first 30 minutes.

**pH Determinations**—Fig. 2 and Table II show the range of the pH of respective samples. The fasting contents varied from pH 1.18 to pH 8.0. In twelve of the eighteen, the pH was below 3.0. Although the fasting contents showed such low pH values, the acidity of all the specimens was reduced by the buffering capacity of the amigen solution to a pH above 4.0. This level was maintained in all cases for not less than 20 minutes and in thirteen of the eighteen for a period of thirty minutes. At this time, only one

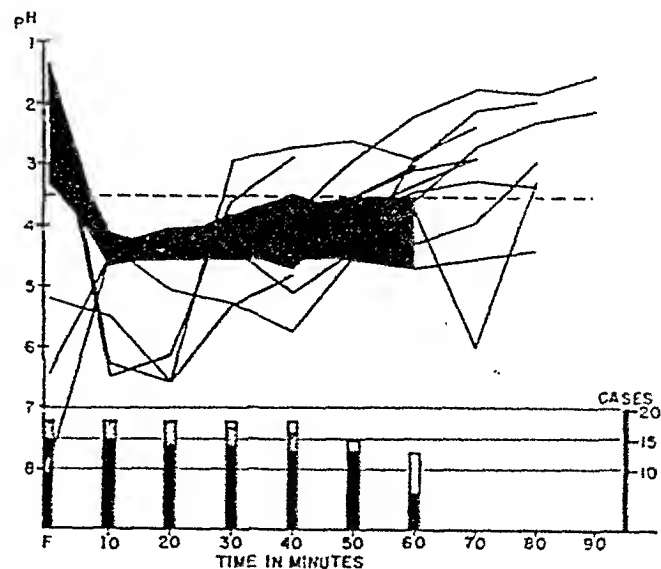


Fig. 2. pH values of gastric samples from Group II (Table II.) Vertical bars represent number of cases for each time interval. Solid bar = values within broad solid curve; cross-hatched bar = values above 3.5 which are not included within solid curve; open bars = values below 3.5. Broad solid curve represents from 71%-87% of cases up to 50 minutes. Note the prompt elevation of pH at 10 minutes even in cases with a fasting pH below 2.0.

chloric acid is equivalent to a 0.0003 M. concentration of hydrogen ion and so called "free acidity" is no longer present. The average pH value of the first specimens in which titratable free acid was determinable after the introduction of the amigen solution was 3.44, which approximates this theoretical value.

Any preparation which would control gastric acidity

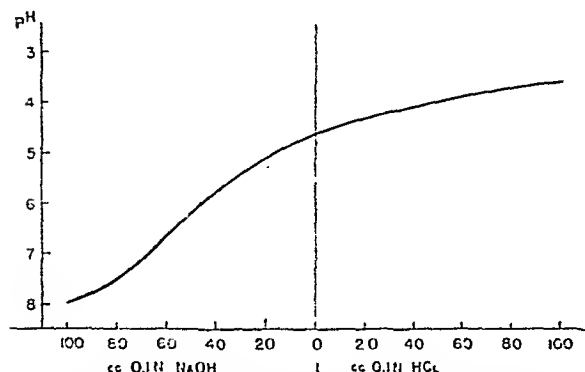


Fig. 3. Potentiometric titration curve demonstrating the buffering capacity of 100 cc. 10% amigen solution in distilled water. (Leeds and Northrup—Universal pH meter.)

is of practical importance in the management of peptic ulcer. It is recognized that uncontrolled gastric acidity plays a part in the production of an ulcer and interferes with its healing. Since it disappears from a solution at a pH of 3.5, free acid would no longer be a serious factor at this point or higher. The part played by pepsin must also be considered. Hollander (3) states that complete inactivation of pepsin is not

obtained until the pH is elevated to 5.0 and that between 4.0 and 5.0 there is no more than 10% of the maximum proteolytic activity of pepsin remaining. Values within this range are readily obtained with the amigen solution (Fig. 2 and Chart II.) This would be expected because of the marked buffering capacity (Fig. 3) of the constituent amphoteric molecules.

This preparation is, in addition, a potential source of amino nitrogen for body metabolism (1.) It is of interest that none of the normal subjects who received this mixture experienced any untoward effects; in fact, there was not even the slightest discomfort. As a result of these observations, the use of amigen in the management of bleeding peptic ulcers is being investigated and will be reported upon in the near future.

### CONCLUSIONS

1. An amino acids mixture (amigen) is an effective buffering agent when introduced into the stomach. The pH values as determined in 18 subjects are well within that range of pH in which free acid is not present and peptic activity is reduced to a minimum.
2. This mixture can be given safely to normal individuals without even the mildest discomforts.
3. It is suggested that amigen may be used in the clinical management of peptic ulcer, even in the presence of bleeding.

### REFERENCES

1. Elman, R. and Weiner, D. O.: "Intravenous Alimentation." *J. A. M. A.*, 112:796, March 4, 1939.
2. Elman, R.: Parenteral Replacement of Protein with the Amino Acids of Hydrolyzed Casein. *Ann. Surg.*, 112:594, Oct., 1940.
3. Hollander, Franklin: *Am. J. Dig. Dis.*, 6:127, 1939.

## The Use of Sulfaguanidine for Ulcerative Colitis\*

By

MANFRED KRAEMER, M.D.†  
NEWARK, NEW JERSEY

SINCE the introduction of the Sulfonamide drugs there has been a hope of finding one that would destroy or vitiate those organisms normally present in the bowel which, regardless of etiology, continue the infection in ulcerative colitis.

With this end in view, Barger (1) and Collins (2) introduced the sulfa drugs in the treatment of ulcerative colitis. Sulfathiazole was the most efficacious and best tolerated of those I tried. After Lyon (3) suggested the possibilities of Sulfaguanidine for bacillary dysentery, I employed it for ulcerative colitis. The rarity of ulcerative colitis and the variation in its clinical manifestations made unsatisfactory the alternate case method of studying the drug, and its value in this disease could only be judged clinically. I hope to convey to the reader my impression that the drug has clinical value.

My observations confirm those of Firor and Poth (4) that despite the high concentrations of the drug

which were obtained in the colon nothing approaching sterilization of the colon contents occurred. We were able to obtain positive stool cultures for streptococci and colon bacilli with a concentration of sulfaguanidine as high as .8 grams per 100 grams of stool. Firor and Poth using animals were able to grow colon bacilli from stools consisting almost entirely of sulfaguanidine.

I have used sulfaguanidine in sixteen cases that have been followed from six to sixteen months. In addition to using sulfaguanidine, a regimen previously described (5, 6) for treating ulcerative colitis, was followed. Although we were unable to sterilize the stools, in eleven of the cases results were excellent, in two cases questionable, in that the sulfaguanidine did not bring about prompt arrest of symptoms, but the colitis gradually was brought under control. In two cases no benefit of any kind was evident. In one case there was such marked suppression of leucocyte formation that the drug had to be discontinued, though the colitis was markedly benefited. In three cases mild, and in two cases severe, skin reactions occurred.

\*From the Department of Gastro-Enterology, Presbyterian Hospital in Newark, New Jersey.

†Visiting physician.

Submitted May 20, 1942.

One of these patients developed a generalized vesiculopustular eruption of the entire body. After a few months, when, during an exacerbation of the colitis, the drug was again given but in smaller dosage, no skin lesions were observed. The other patient with a severe reaction developed a maculo-papular rash and intense headache which disappeared on discontinuance of the drug, but reappeared within forty-eight hours on doses as small as one gram per day. It was noted that unless and until stool concentrations of about five hundred mgm. per 100 grams of stool were obtained, little benefit could be expected from the use of sulfaguanidine. Obviously the more frequent the movements the harder it was to get adequate stool concentrations. Adults were given from six to twelve grams of the drug a day for periods of several weeks. In no case was a blood level of more than 1.5 mgm. per cent obtained though urine levels of forty mgm. per cent were not unusual and crystals were frequently seen in the urine. The low blood levels are the result of rapid excretion in the urine rather than as was first thought, of poor absorption from the bowel (4). Blood smears were examined three times per week whenever sulfaguanidine was used.

Results obtained seem to me to justify a trial of sulfaguanidine for every case of ulcerative colitis. If it proves helpful it should be employed at the earliest sign of an exacerbation and also whenever the patient has an upper respiratory infection. The latter often initiate bouts of colitis. By observing simple precautionary measures, toxic manifestations can be recognized early, and use of the drug should be discontinued temporarily. Sulfaguanidine is non-specific and probably is valuable only because it cuts down on the secondary invaders in the colon giving the mucosa a chance at self restoration.

## REFERENCES

1. Brown, A. E., Herrell, W. E. and Barzen, J. A.: Neoprontosil (Oral) in the Treatment of Chronic Ulcerative Colitis. *Proc. Staff Meet., Mayo Clinic*, 18:562, Sept. 7, 1938.
2. Collins, E. N.: Use of Sulfanilamide in Chronic Ulcerative Colitis. *Cleveland Clin. Quart.*, 5:16, July, 1938.
3. Lyon, G. M.: Chemotherapy in Acute Bacillary Dysentery. *West Virginia Med. J.*, 37:54, Feb., 1941.
4. Firor, W. M. and Poth, E. J.: Intestinal Antisepsis with Special Reference to Sulfaguanidine. *Ann. Surg.*, 114:663, Oct., 1941.
5. Kraemer, M. and Asher, M.: The Management of Idiopathic Ulcerative Colitis. *J. of the Med. Soc. of N. J.*, 32:275, May, 1935.
6. Kraemer, M.: Ulcerative Colitis and Its Management. *Rev. of Gastro-Enterology*, 8:357, Sept.-Oct., 1941.

## Editorials

### HOW VITAMINS AFFECT THE BODY'S METABOLISM

THE University of Chicago Press has recently published a fine report of a symposium on the biological action of the vitamins.\* This little volume will interest every thoughtful physician who would like to get an idea of what is known today of the way in which the vitamins work, that is, what chemical functions they facilitate. As Dr. Elvehjem pointed out in the first paper, everyone is now willing to admit that many of the deficiency diseases in both men and animals are due to a lack of several vitamins. As yet little is known about the action of Vitamin A. Little is known also of how Vitamin D affects calcification. Vitamin C appears to have much to do with the formation of the intercellular tissues. Vitamin E has much to do with the function of the pituitary gland.

Very interesting are the discoveries which have shown something of the relationship between the vitamins, the hormones, and the ferments and co-ferments. This series of papers brings out the fact that one of the best and simplest ways of studying vitamins is to see how they facilitate the growth of bacteria and yeast. Most physicians think of Vitamin B<sub>1</sub> as concerned primarily with the healing of nervous tissue, and the newspapers would have us believe that it is the "Morale vitamin." Actually, it can be shown to have marked influence on the growth of microscopic bacteria which have no nervous system at all, and which probably are not concerned about morale or the War in Europe.

Very interesting is the way in which some of the vitamins act as prosthetic groups for enzymes. Lack of Vitamin A causes a pronounced fall in the esterase content of the blood serum. Vitamin C affects the function of many proteolytic and oxidizing enzymes

and it plays a rôle in the metabolism of plants. Nicotinic acid appears to function as a precursor of several co-enzymes.

Diphosphothiamine is a catalyst for the oxidation of pyruvic acid, and thus it helps in the metabolism of carbohydrate much as insulin does. All of which suggests that perhaps chemists will some day discover a substance that will take the place of insulin. Recent studies indicate that thiamine is necessary for the synthesis of fatty acids from carbohydrate, and this action is probably secondary to its effect on the oxidation of pyruvic acid. Thiamine helps in the synthesis of acetylcholine.

Helpful to the clinician may be the statement of Jolliffe that the addition of thiamine to an experimental diet, which in volunteers had produced a neurasthenic syndrome, caused all symptoms to disappear within three days. This would suggest that when a patient, stuffed for weeks with thiamine, fails to show any pronounced improvement, the probability is that his symptoms are not due to a deficient diet.

Interesting is the discovery that the measurement of the amount of pyruvic acid in the blood is a good test for thiamine deficiency. From this it is to be hoped that some day, instead of stuffing all our patients with vitamins, we will do a few tests on the urine or blood to see whether they really need this medication. Certainly the practice of medicine will then become more scientific.

Of interest to clinicians is the discussion by Dr. Sebrell of riboflavin deficiencies. The symptom most likely to be noticed is the appearance of linear fissures at the angles of the mouth. In bad cases there is a vascularized keratitis with photophobia. It is remarkable that this type of deficiency is not seen more often because the amount of riboflavin to be found in most common foods is very small. The best sources of

\*The Biological Action of the Vitamins. A symposium edited by E. A. Evans, Jr., Univ. Chicago Press, Chicago, \$3.00.



supply are liver, yeast, kidneys, milk, cheese and eggs.

David Smith pointed out that the intake of nicotinic acid needed by men and women is small. As he says, if a person is free from serious gastro-intestinal disease, the consumption twice a week of a meal containing red meat or fish will prevent the coming of pellagra even if the rest of the diet is deficient.

Interesting is the discovery that choline is of great importance in the diet of growing animals. It has much to do with the metabolism of the methyl radical, and its absence from the diet is likely to produce severe metabolic disturbances. W. C. A.

### THE NEUROGENIC PRODUCTION OF DUODENAL ULCER

**T**HE psychosomatic aspect of peptic ulcer gains credence daily. Whether acute or chronically recurrent psychic traumas initiate the ulcer *de novo*, or whether these stimuli activate phases of recurrent activity in an ulcer already formed, remains as yet a point of disputation. The hypothalamus is important as a center for the control of the autonomic nerve centers; its influence dominates the functions of the sympathetic systems, particularly those of the alimentary tract, including secretion, motility, and vasomotor control. Such relations can be demonstrated by experimental methods and have been substantiated to some degree by clinical observations and by pathological data.

The hypothalamus is probably also an important coordinating center for the emotions. Ranson, by stimulating the posterior hypothalamus, produced in animals, clawing, biting, struggling, and all the associated evidences of intense rage. The hypothalamic electrode of Grinker, when passed through the nose into the base of the sphenoid sinus, produced upon stimulation, well-defined changes in nervous activity associated with sobbing, anxiety, depression and much fear. Tumors involving the hypothalamus produce psychic depression with loss of inhibitions manifested in the sphere of social conduct and polite behavior.

Be it through a cerebral neoplasm, an electrical stimulus, or recurring psychic traumas, the effect of such disturbance upon the hypothalamus is the production of an emotional imbalance, plus a derange-

ment in the physiological control of the sympathetic functions of the alimentary and other tracts.

Somehow, through paths as yet not accurately ascertained, we can begin to visualize the creation of a peptic ulcer. From the cortex to the hypothalamus, to the red nucleus, to the centers in the medulla—hence by the efferent outflows in the vagal and sympathetic systems, these are the likely pathways, but the details are lacking.

In the case reported by Moolten (1), an acute duodenal ulcer of the type characteristically human, caused death seventeen days following a severe crushing injury to the spinal cord. A youth of 16 years dived into shallow water and sustained a compression fracture of the bodies of the 5th and 6th cervical vertebrae, with resultant compression of the spinal cord. This injury of the spinal cord obviously supplied the mechanism for the production of a duodenal ulcer with ensuing fatal hemorrhage from an eroded artery.

The author discusses the *modus operandi* of ulcerogenesis in his case in terms of vago-sympathetic asynergia. According to him, the sympathetic pathways in the cord, interrupted by the crush injury, permitted the vagus system unopposed dominance culminating in the formation of the ulcer.

This vagostimulatory type of ulcer would thus provide pathological confirmation for such experimental observations as ulcer following "prolonged administration of acetylcholine, prolonged electrical stimulation of the vagi, severance of the splanchnic nerves or extirpation of the celiac plexus and the intraventricular injection of pilocarpine."

Whatever may be the neurogenic mechanism in the production of such an ulcer, here is a human being whose spinal cord has, in effect, been pithed in the upper cervical segments; this "spinal animal" survived seventeen days and died of hemorrhage from a duodenal ulcer.

The proponents of the psychosomatic theory of the etiology of ulcer may have found here the neurogenic mechanism by which psychic traumas are conveyed over nerve pathways (vagal presumably), eventually to produce a typical ulcer. Burrill B. Crohn.

### REFERENCE

1. Moolten, S. E.: *J. Mt. Sinai Hosp.*, VIII-565, 1942.

## Abstracts of Current Literature

FRANKLIN HOLLANDER, Associate Editor in Charge of Abstracts, New York, N. Y.

ALBERT CORNELL, New York, N. Y.  
MAURICE FELDMAN, Baltimore, Md.  
CHARLES A. FLOOD, New York, N. Y.  
M. H. F. FRIEDMAN, Philadelphia, Pa.  
J. DUFFY HANCOCK, Louisville, Ky.  
THOMAS A. JOHNSON, Philadelphia, Pa.  
ALLEN A. JONES, Buffalo, N. Y.  
N. W. JONES, Portland, Ore.  
HENRY H. LEINER, Boston, Mass.  
PHILLIP LEVITSKY, Montreal, Can.

JESSIE LOVE, Louisville, Ky.  
FRANZ J. LUST, New York, N. Y.  
IRA A. MANVILLE, Portland, Ore.  
ARTHUR E. MEYER, Brooklyn, N. Y.  
W. M. MOREHEAD, Milwaukee, Wis.  
J. R. ry, Indiana  
uiscville, Ky.  
N. J.  
Detroit, Mich.

RUDOLF SCHINDLER, Chicago, Ill.  
MICHAEL SHUTKIN, Milwaukee, Wis.  
VIRGIL E. SIMPSON, Louisville, Ky.  
H. J. SIMS, Denver, Colo.  
HENRY TUMEN, Philadelphia, Pa.  
ROBERT TURELL, New York, N. Y.  
EDGAR WAYBURN, San Francisco, Calif.  
JOHN WILLARD, Philadelphia, Pa.  
C. WILMER WIRTS, Philadelphia, Pa.

[Microfilm copies of papers may be obtained from Microfilm Service of the Army Medical Library at 25¢ for each complete article, not exceeding 25 pages in length—and 10¢ for each additional 10 pages or fraction thereof. Prepayment is not requested. Remittance may be made with subsequent orders and in such manner as found most convenient. Address—Microfilm Service, Army Medical Library, Washington, D. C.]

### CLINICAL MEDICINE MOUTH AND ESOPHAGUS

WU, Y. K. AND LOUCKS, H. H.: *Surgical Treatment of the Esophagus. Chinese Med. J.*, 60:1, July, 1941.

This paper consists of a scholarly review of the methods and results of resection for carcinoma of the esophagus, and of a report of the author's own cases, of which two survived and one died.

The authors report the interesting fact that, for some undetermined reason, carcinoma of the esophagus is especially prevalent among the Chinese. According to statistics from 1937, this lesion constitutes 51% of all neoplasms of the alimentary tract, exclusive of those involving the oral cavity and pharynx, seen in the Peking Union Medical College. Like everywhere in the world, the number of patients with early carcinoma of the esophagus, suitable

## The Treatment of Intestinal Disorders in the Military Forces\*

By

L. C. GATEWOOD  
CHICAGO, ILLINOIS

SINCE the beginning of military medical history the occurrence of intestinal disorders among the armed forces has always been an important problem. Hurst (1) states that out of 30,000 British soldiers in the Crimea 7,833 suffered from dysentery and 2,143 died of this condition. In World War I the disease appeared in Germany in 1914 and headed the list of infectious diseases with 155,000 cases. The British army in France presented its maximum incidence in September, 1916, with 126 cases per 100,000 but reached 2,900 cases per 100,000 in Mesopotamia. It is of interest to note that in the East the frequency of the Shiga and Flexner types was about equal whereas in the West the Flexner type made up 85% of the total.

It is too early for data to be available concerning the occurrence in the present war but it may reasonably be expected that the incidence will be comparable to that which has occurred previously. In addition to bacillary dysentery we may reasonably expect a variety of other intestinal disorders, the types to be encountered depending to a large extent upon the location. Our forces will be serving in all parts of the world. Many will be on duty in tropical and subtropical areas where types of intestinal disease are found which are not usually encountered in the United States. As troops are transferred from one theatre of war to another and disabled soldiers and sailors are returned from combat zones to the hospitals in the United States we may expect that diseases which are endemic in these far places will be to a greater or lesser extent transplanted here. We must therefore anticipate a wider range of diagnostic possibilities than ever before, both at home and abroad.

An outstanding difference between army and civilian practice lies in the fact that it is continually necessary to evacuate patients from those hospitals nearest the zone of combat to other hospitals farther to the rear in order to make place for new arrivals from the battle area. As a result the patient is likely to pass within a relatively short time under the care of several different physicians (medical officers.) It becomes therefore exceedingly important to recognize the potentialities of the various therapeutic agents available, their limitations and their possible toxic effects. It is likewise especially important that all those caring for such patients accurately record what treatment has been instituted, what drugs have been used, in what dosage and over what period of time. Not long ago I had occasion to see a nurse patient in whom a diagnosis of amebic dysentery had been made. She had been admitted to one hospital where she had been given a series of injections of emetine. Shortly afterward she was transferred to another hospital where emetine was again administered. She arrived at the third hospital with a severe paralysis of both legs. She had been fitted with braces for her knees and with

these she was barely able to get about with the aid of crutches. Unfortunately the neurologist who examined her had failed to recognize the relationship between the trouble in her legs and her anti-amebic therapy and the treatment had gone merrily forward. She was fortunate to be alive. Unless careful attention is paid to the toxic effects of the drugs used and careful notations made on the patient's record such incidents may be multiplied.

It is probable that in most zones *bacillary dysentery* will be the chief source of disability, the predominating type varying in different locations and possibly in the same location at different times. The outstanding advance in the therapy of this condition has been the introduction of drugs of the sulfonamide group, especially sulfaguanidine. It is as yet too early to evaluate this drug. Reports thus far available (2, 3, 4) indicate that it is more effective than any of the drugs previously available. They are not entirely in agreement as to the extent to which the drug is absorbed but indicate that it is less toxic than most of the other sulfonamides. Reports are not yet available on the results obtained with the most recent member of this group—sulfasuccidine.

Of the protozoal forms of diarrhea, that due to the *entameba histolytica* is by far the most prevalent and the most important. It is endemic in all parts of the world but the forms encountered in the tropics are as a rule more severe than those usually seen in temperate zones. Conditions encountered in field service are especially favorable for the development of severe dysenteric manifestations. It is particularly in this type of case that emetine has for a long time been recognized as a highly effective remedy, having been used very extensively in the British service in India. Of all the therapeutic agents available in this disease, it is, however, the most toxic. It is not wise to exceed a dosage of one grain per day and not more than 12 grains in one series nor in any period of a month. It is a cumulative poison, only slowly excreted from the body and its greatest danger lies in its effect upon the myocardium where it causes acute degenerative changes. Unfortunately there may be little or no warning of the cardiac effects and I have seen a patient die suddenly within 3 hours of the first complaint of cardiac embarrassment. Evidence of organic disease of kidney or of myocardium should be regarded as a contra-indication to the use of emetine. Less serious but nevertheless decidedly unpleasant is the effect upon the locomotor system, resulting in paralysis of the legs and less commonly of the arms. There has been some controversy over the question whether this effect is due to a toxic neuritis, as was originally believed, or to a toxic myositis as contended by Young and Tudhope (5) who were unable to find pathological evidence of neuritis and who therefore attributed the symptoms to toxic effects upon muscle.

\*Read at the Annual Meeting of the American Gastro-Enterological Association at Atlantic City, N. J., June 8, 1942.

On at least one occasion I have observed mental symptoms including hallucinations, delusions and disorientation in an individual who had developed paralysis of his legs while on emetine therapy. The clinical course of the disease on treatment was not readily compatible with the assumption of cerebral localization of the organism and the condition was much more readily explainable as a simultaneous involvement of nerve structures in the legs and the central nervous system. Manifestations of this type require commonly from three to six months for complete recovery. The maintenance of a generous store of thiamin within the body has seemed to be of some value in protecting against the development of manifestations of this type.

The arsenical group including carbarsone, acetarsone or stovarsol and treparosone have proved effective forms of anti-amebic therapy. While far less dangerous than emetine they are by no means free from the risk of arsenical intoxication. The symptoms are those common to other forms of arsenic poisoning and include renal, hepatic and dermatologic manifestations. It has frequently been stated that a tolerance to arsenic is acquired as a result of prolonged administration but in recent years some controversy has arisen concerning the factors or mechanism involved and the question whether there was a true increase in tolerance or a change in absorption. Much less discussion has been devoted to the opposite phenomenon—an apparent sensitization. On several occasions we have observed that a patient who had previously taken full doses of one of the arsenicals with no untoward manifestations suddenly developed acute toxic symptoms after only a small amount of the same drug had been administered in a subsequent period of therapy. Delp (6) has recently called attention to the relation of Vitamin C levels to arsenical sensitivity. Further evidence will be necessary before this can be fully evaluated but meantime it should not prove amiss to provide an adequate intake of ascorbic acid for patients receiving arsenical therapy.

The drugs of the iodoxy-quinoline group (vioform, chiniofon, diodoquin, etc.) have proved especially valuable in the treatment of amebiasis because of the fact that they are practically free from toxic effects. Some of these drugs may, in susceptible individuals, cause diarrhea and gastric irritation but so far as is known there have been no serious toxic manifestations and the amebicidal effectiveness of drugs of this group is only slightly less than that of the arsenical group. The best results are usually obtained by alternating the various types of therapy.

*Balantidium coli* as a cause of diarrhea is occasionally encountered in the southern part of the United States and is of frequent occurrence in tropical zones including India and Indo-China, the Philippines, Egypt and North Africa. Most of the drugs which have been used in the treatment of amebiasis have been tried in this condition. For each of them some beneficial results have been reported but none of them have proved uniformly effective. The dangers of toxic effects would be those previously discussed.

Infestation with *Girardi intestinalis* is frequently found in this country as a relatively asymptomatic condition. However, this organism may occasionally give rise to severe and persistent diarrhea and this is more likely to be true in certain of the tropical and subtropical theatres of war. It is difficult to appraise

the value of any of the many drugs which have been used because of the great variability in the activity of the parasite. Atebrine is probably the most effective remedy. Most of the data concerning the toxicity of this drug have been collected from those areas in which it has been widely used in the treatment of malaria.

*Malarial dysentery* is of common occurrence in tropical areas and may resemble cholera in its severity. It is characterized pathologically by intense infection of mucosal cells with parasites or parasitized cells, necrosis of the epithelium, leucocytic invasion of tissues adjacent to necrotic zones and the invasion of necrotic tissues by bacteria. These conditions are as a rule effectively treated with quinine but because of possible shortage of this drug it may be necessary to have recourse to other remedies. Both atebrine and plasmoquin have been found effective. It is difficult to clearly separate the toxic effects of these drugs from the symptoms of the disease, including as they do epigastric pain, headache, dizziness, drowsiness, etc. Atebrine is very slowly excreted and traces of the drug have been identified in the body as late as 65 days after the last administration. The drug may cause a yellow coloration of the skin due to a deposit of the drug in the skin. It is also recognized that the drug may cause liver damage when continued over a long time.

The diarrheas of *schistosomiasis* and of the later stages of *leishmaniasis* are most effectively treated with antimony in one of its various forms. This drug is effective as an anti-protozoal agent only by the parenteral route. When given by mouth it causes nausea and vomiting and it is only very slowly absorbed from the gastro-intestinal tract. When given parenterally it is as a rule completely excreted by the kidneys in 3 to 5 days. The toxic symptoms which may occur include the rather prompt development of an irritating cough and the not infrequent occurrence of a type of pneumonia which is recognized pathologically as due to the drug and not a complication of the primary disease. Other toxic symptoms may include joint pain or acute arthritis, liver damage and cardiac manifestation including especially bradycardia. It is noteworthy that in some regions the occurrence of serious intoxication has been reported in as many as 15% of the patients treated with this drug.

In taking stock of our armamentarium for the treatment of intestinal diseases among the armed forces it is fortunate that we are not faced with a serious shortage of any of the essential drugs except possibly quinine and in the involvement of the gastro-intestinal tract this can be very largely replaced by the synthetic remedies atebrine and plasmoquin. Emetine is imported in considerable quantities from South America and adequate stocks are on hand. The other remedies required are obtainable from our own laboratories.

## REFERENCES

1. Hurst: Medical Diseases of War, 1941.
2. Marshall, E. K., Jr., Bratton, A. C., Edwards, Lydia B. and Walker, Ethel: Sulfanilylguanidine in Treatment of Acute Bacillary in Children. *Bull. Johns Hopkins Hosp.*, 68:94, 1941.
3. Marshall, E. K., Jr., Bratton, A. C., White, H. J. and Litchfield, J. T., Jr.: Sulfanilylguanidine: A Chemotherapeutic Agent for Intestinal Infections. *Bull. Johns Hopkins Hosp.*, 67:163, 1940.
4. Lyon, G. M.: Chemotherapy in Acute Bacillary Dysentery. Part II. Clinical Use of Sulfanilylguanidine. *West Virginia M. Monthly*, 37:54, 1941.
5. Young and Tudhope: Pathology of Prolonged Emetine Administration. *Tr. Royal Soc. Trop. Med. and Hyg.*, 20:93-99, 1926.

6. Delp, Mahlon: Ascorbic Acid in the Treatment of Arsenical Dermatitis. *J. Kansas M. Soc.*, 42:519, 1941.

### DISCUSSION

DR. DWIGHT M. KUHNS (Lt. Colonel Medical Corps, Commanding Officer, Fourth Service Command Laboratory, Fort McPherson, Georgia.) It gives me great pleasure to be here today, and to have the privilege of discussing Dr. Gatewood's excellent paper. Little can be added to his comprehensive analysis of intestinal disorders. My attention has been focused on the diarrheal diseases, since all positive cultures isolated from cases of diarrhea in the Fourth Service Command have been sent to the Fourth Service Command Laboratory for confirmation.

The occurrence of a high incidence of diarrhea and dysentery in the Army, especially in troops on maneuvers, has become a problem of particular interest to the Army Medical Corps. During the past year many cases of diarrhea have been admitted to Army hospitals, but the majority have been ambulatory patients. Patients that are not sufficiently ill to be hospitalized present a more dangerous situation, since the possibility of transmitting the disease to others is more likely in patients that are not properly isolated and treated. With the modern knowledge of the control of diarrheal diseases it was surprising to find a high incidence of cases of this type among our troops in training last year.

An important part in the solution of this problem is the training of our Commanding Officers in the realization of the importance of sanitary control measures. Doctors assuming duty with the Army must realize the existence of this danger and the necessity for rigid adherence to the sanitary measures recommended by the Sanitary Field Manual and Army Regulations. The rapid mobilization of an Army presents many problems in the control of communicable diseases. It is necessary, therefore, that every possible step be taken to train the Doctors who are becoming our Medical Inspectors, the Troop Commanders, and the troops themselves in the simpler methods of prevention of diarrheal infections which are transmitted mainly through food, flies, fingers, water and milk supplies.

During the Louisiana and Carolina maneuvers last year, 233 cases of diarrhea admitted to Station Hospitals were cultured for pathogenic enteric organisms. *Shigella sonnei* was the most common organism found, occurring in 76

cases, and *Shigella paradysenteriae* ranked second in prevalence, occurring in 71 cases. Of the latter, W, X, and VZ were more prevalent than the other types. There were no *Shigella dysenteriae* (Shiga) found and amoebic dysentery was practically non-existent.

The Surgeon General has taken an active interest in this problem and has instituted various methods of control. The investigation of the prophylaxis of these diseases has been assigned to a group of civilian investigators who are making every effort to find an immunization agent. The development of a prophylactic agent for diarrheal diseases is a difficult problem because of the wide variety of bacteria that have been incriminated. The solution of this problem would be of an inestimable value in protecting troops assigned to endemic areas.

Effective control and treatment of diarrheal diseases depend to a large extent upon early diagnosis, which can be accomplished only by quick isolation and identification of intestinal pathogens. Plans have been formulated in the Fourth Service Command for the institution of a bacteriological control program as a part of the general plan for the prevention of these diseases. This program includes the culturing of all cases of diarrhea and the use of the improved inhibitory media. In addition, all Station Hospital Laboratories in the Fourth Service Command will be required to examine and report on known cultures submitted to them from the central Fourth Service Command Laboratory. Where deficiencies in laboratory services are found, laboratory technicians will be sent to the central Laboratory for training in the bacteriological and parasitological examination of stools.

The sulfonamide drugs, particularly the newer derivatives such as succinyl sulfathiazole, offer considerable promise in the treatment of diarrheal diseases. Reports from various military units indicate that where sulfathiazole and sulfaguanidine and anti-dysentery sera have been used in alternating cases, sulfathiazole seems to shorten the duration of the disease and relieve the symptoms sooner than any other of the drugs under therapeutic trial.

The chief problem in the Army is to prevent the occurrence of diarrhea, or to stop an outbreak in its incipient stages before it has reached epidemic proportions. For these reasons, the Army personnel must be trained in fundamental safeguards in sanitation and must practice hygienic measures even under the most adverse circumstances of field operations.

## Relationship of the Hypothalamus to the Large Bowel

By

DONAL SHEEHAN, M.D.\*

MY interest in the central nervous regulation of the gastro-intestinal tract from the hypothalamus began in 1933 when I assisted Dr. John Beattie in some experiments on gastric motility following hypothalamic stimulation (1). The modified hemi-decerebration method of exposing the hypothalamus was used, splitting the corpus callosum in the midsagittal plane and approaching the floor of the third ventricle from above. In the light of more recent work (6) with the stereotaxic instruments, the approach used was not an ideal one, but it had the advantage that no further anaesthetic was necessary, after the initial

dose of chloralose given several hours before stimulation. Unipolar faradic stimulation, by means of the Harvard inductorium, was carried out in cats, in the supraoptic, infundibular and mammillary regions of the hypothalamus. Pressure changes in the stomach were recorded from an oesophageal catheter, the "resting" stomach filled with 100-150 cc. warm saline.

Under these conditions stimulation of the "anterior" regions of the hypothalamus resulted in a rise in intra-gastric pressure, with a subsequent increase in rhythmic contractions of the stomach, and accompanied by narrowing of the pupil and a fall in blood pressure. Stimulation of the "posterior" hypothalamus on the other hand was followed by dilatation of the pupil, a rise in blood pressure and a slight fall in

\*From the Department of Anatomy College of Medicine, New York University.

Read at the Annual Meeting of the American Gastro-Enterological Association, Atlantic City, N. J., June 8, 1942.

intra-gastric pressure with obliteration of gastric motility.

Despite the lack of refinement in technique, the results, particularly those from anterior hypothalamic stimulation, were confirmed by Heslop (2) four years later, using cats and dogs under chloralose anaesthesia. Bipolar electrodes were inserted into the hypothalamus by the stereotaxic instrument, and the stimulus ( $\frac{1}{2}$  volt at 50 impulses per sec.) was produced by a thyatron valve stimulator. The observations on gastro-intestinal motility were made fluoroscopically after the introduction (in every animal) of 20 cc. of a thin barium paste through a tube into the stomach. In the control animals barium appeared in the upper intestine about 60 minutes after it was introduced into the stomach. Following stimulation in the anterior (supraoptic) region a change in peristalsis was observed in one minute. The waves became deeper and followed each other with greater frequency, usually about every 15 seconds. Within about 15-20 minutes after the barium introduction, it was usual to detect the opaque substance in the small gut, and at 30 minutes it was present in considerable quantity.

Using essentially the same technique, 3 years earlier, Ranson and his colleagues (5) had confirmed the inhibition of motility and fall of gastric tone which Beattie and Sheehan had observed following posterior hypothalamic stimulation. Ranson located the center more particularly in the *lateral hypothalamic area*. In a cross-section, whether anteriorly through the supraoptic region, or half way back through the infundibular region, or posteriorly through the mammillary region, we can recognize two general parts—a *medial* and a *lateral hypothalamic area*. The median lies close to the floor of the III ventricle. The lateral extends throughout the entire length (anteroposteriorly) of the hypothalamus, and through it runs the median forebrain bundle. The principal localization of the "center" for sympathetic control would appear from all experimental evidence to lie here—within the lateral hypothalamic area. It is from stimulation of this area that we obtain the inhibition of peristaltic activity. The excitatory responses in gastro-intestinal motility, described in the early part of this paper, were all obtained by stimulation farther forwards—in the *anterior parts of the supra-optic region*, and also, as Ranson has shown—in that part of the grey matter immediately in front of it—located near the anterior commissure—and known as the *preoptic region*. Wang, Clark, Dey and Ranson (7) (1940) have recently observed the intestinal movements directly through a window of transparent film sewn into the abdominal wall. Kymographic records of intestinal and colonic activity were made in some animals. Faradic stimulation of the hypothalamus was carried out with the aid of the Horsley-Clarke stereotaxic instrument. When the anterior hypothalamus (supra-optic region) was stimulated for a period of 15-60 seconds, there appeared some blanching of the small intestine, followed by, and sometimes *after cessation* of stimulation, swinging movements in the small intestine, with segmentation and occasionally peristalsis. The colon appeared to be more responsive, and peristaltic waves were more frequently observed. The latent period varied between 40 and 60 seconds. The response usually lasted about 5 minutes. This is therefore relatively a

*delayed* and prolonged response. Sometimes, however, the tone of the intestine and colon was raised promptly (within 7 seconds of stimulation) and increased movement lasted only during the period of stimulation. This *immediate* response was usually evoked from an area of the hypothalamus situated dorsally and caudally to the reactive region for the delayed response. In rare cases a combined response of immediate and then delayed excitation was encountered. Vagotomy in 3 animals abolished the immediate but not the delayed response.

The *immediate* response, abolished by vagotomy, is similar in many ways to the excitatory effects on the stomach reported by Beattie, and a neural mechanism is definitely suggested. The *delayed* excitatory response which was obtained in several vagotomized animals, suggests a different mechanism, possibly hormonal through activation of the pituitary.

Wang et al (7) rarely observed any inhibitory effects on the intestine from hypothalamic stimulation, for the animals they used were chiefly in the resting condition. Masserman and Haertig (4) (1938), using a rather similar technique, observed both excitation and inhibition of intestinal activity, the former by a relatively *weak* stimulus in the *anterior* portion of the hypothalamus, the latter by the application of a *strong* stimulus *anywhere* in the hypothalamus.

Dr. S. L. Felder has been working with me on this problem during the past year, with special reference to the activity of the large bowel. The work is still in progress and our results are not yet complete, but we have considerable evidence of the inhibitory effect on the colon from hypothalamic stimulation.

We have used cats in the "waking state" following nembutal anaesthesia. Bipolar electrodes have been implanted into the hypothalamus by means of the Horsley-Clarke stereotaxic instrument, and the stimulus supplied through a Harvard inductorium and later by a thyatron stimulator. Colonic activity has been recorded kymographically by means of a balloon inserted through the rectum for a distance of 5 inches from the anus. The balloon was distended in each experiment with 15-20 cc. air, so that a pressure of 5-8 cc. water was obtained.

The initial activity of the colon varied considerably, despite a regulated diet and regimen for several days prior to the experiment. We have been successful in initiating activity in a quiescent colon in only two instances and in each case stimulation was made in the preoptic region. The excitation appeared after stimulation had ceased and persisted for some minutes. It therefore resembled the *delayed* effect described by Wang et al (7). We have not yet observed the *immediate* excitatory response in the colon.

Inhibition of all activity within the colon, on the other hand, was a common result from stimulation anywhere within the hypothalamus, either anteriorly in the supraoptic area or posteriorly in the mammillary region. We were usually about 2 mm. from the mid-line, within therefore the lateral hypothalamic area. The inhibitory response is an immediate one, and rhythmic activity returns fairly promptly after cessation of stimulation. The stimulation produces other sympathetic responses, such as dilatation of the pupils and rise in blood pressure, indicating a more diffuse sympathetic discharge. They could still be



evoked several hours after bilateral adrenalectomy, so that a direct neural mechanism is suggested.

In conclusion therefore all observers agree that adequate hypothalamic stimulation, particularly in the lateral hypothalamic area, is followed by inhibition of peristalsis in the large bowel, as well as in the intestine and stomach. Such effects are more marked in the colon than elsewhere. It is interesting to speculate whether the hypothalamus may play a part in the production of Hirschsprung's disease, a disturbance which is apparently central, for it can be interrupted by spinal anaesthesia, and the good result may persist for many months.

There are adequate grounds for accepting a *sympathetic center*, regulating gastro-intestinal activity, located in the hypothalamus, more particularly in the lateral hypothalamic area. The evidence does not warrant a more exact anatomical localization, although the posterior (mammillary) region is perhaps particularly responsive. It must be remembered that the hypothalamus is a very small region, comprising, in the cat, a cube, the dimension of which is approximately 4 mm.

The motor (excitatory) responses of the stomach and intestine following stimulation more anteriorly, in the preoptic and anterior supraoptic regions, are less definite. They are not always reproducible; nor is the causal relationship between stimulation and response always certain. Both immediate and delayed responses may be found, and the latter, at least, is still present after bilateral vagotomy. It is not yet justifiable therefore to assume the existence of a discrete parasympathetic center in the preoptic region.

It may be that cortical inhibitory pathways to the sympathetic center in the hypothalamus are being activated by stimulation. In any event it is questionable whether any real purpose is served in labeling the responses of higher centers as "sympathetic" and "parasympathetic," which after all are specifically manifestations of *peripheral* nerve activity.

Finally, in view of the gastric erosions which we found in an earlier study (3) following hypothalamic injury, we have looked for similar findings in the intestinal mucosa at the conclusion of each experiment. So far we have seen nothing to resemble these in any way, but the extent of hypothalamic injury in our experiments must have been very small.

#### REFERENCES

1. Beattie, J. and Sheehan, D.: *J. Physiol.*, 81:218-227, 1934.
2. Heslop, T. S.: *Quart. J. Exp. Physiol.*, 28:335-339, 1938.
3. Hoff, E. C. and Sheehan, D.: *Am. J. Path.*, 11:789-802, 1935.
4. Masserman, J. H. and Haertig, E. W.: *J. Neurophysiol.*, 1:350-356, 1938.
5. Ranson, S. W. and Magoun, H. W.: *Exptl. Physiol.*, 41:56-163, 1939.
6. Sheehan, D.: *Assoc. Res. Nerv. Ment. Dis.*, 20:589-516, 1940.
7. Wang, S. C., Clark, G., Dey, F. L. and Ranson, S. W.: *Am. J. Physiol.*, 130:81-88, 1940.

#### DISCUSSION

QUESTION: Were any pathological lesions observed in the livers of these animals with hypothalamic injuries?

DR. DONAL SHEEHAN (New York): Some of the livers in these animals showed fatty changes rather typical of fatty infiltration of the liver, but these animals showed other changes in fat metabolism. They may become obese and show an excess intake of food, and therefore it is not certain whether the liver changes are specific or just part of the general process, but Dr. Irving Graef of our Medical School, is working on this particular problem at present.

## Concerning the Influence of Glucose on the Response of the Human Stomach to Test Meals\*

By

HARRY SHAY, M.D., J. GERSHON-COHEN, M.D., D.Sc. (Med.), SAMUEL S. FELS, LL.D.

and

HERMAN SIPLET, A.B.

PHILADELPHIA, PENNSYLVANIA

THE relationship of low blood-sugar levels to gastric secretion is well-established. Insulin has been widely applied in the study of gastric anacidity. Its effect in producing increased gastric secretion is known to be dependent upon the resultant hypoglycemia as well as upon intact vagi. (For literature, see Babkin, B. P. (1)). It has also been suggested that a preprandial low blood-sugar level may be important to the gastric hypersecretion and also to the symptoms in some duodenal ulcer patients. The possible relationship of hyperglycemia to reduced gastric secretion is perhaps less appreciated, although the high incidence of anacidity in diabetes mellitus first stressed by Bowen and Aaron (2) has been reported repeatedly.

Furthermore, Rothenberg and Teicher (3), by a careful statistical study, found a much lower incidence of peptic ulcer in diabetic individuals than in non-diabetic ones. However, glucose in the small intestine could, under certain conditions, influence gastric secretion through two mechanisms; a local action on the bowel mucosa and an elevation of blood sugar. We have investigated these mechanisms in man in this report. We are cognizant of the shortcomings implicit in methods for physiological investigations directly in the human subject. We recognize that our experimental method does not permit accurate measurement of volume of secretion, dilution or evacuation, nevertheless the changes in gastric acidity and evacuation in our experiments are such as to permit deductions which help clarify the problem. More detailed procedures for the human subject have been devised with

\*From the Medical Research Laboratory, Samuel S. Fels Fund and the Gastro-Intestinal Division Medical Service I, Mt. Sinai Hospital, Philadelphia, Pa.

Read at the Annual Meeting of the American Gastro-Enterological Association, Atlantic City, N. J., June 8-9, 1942.

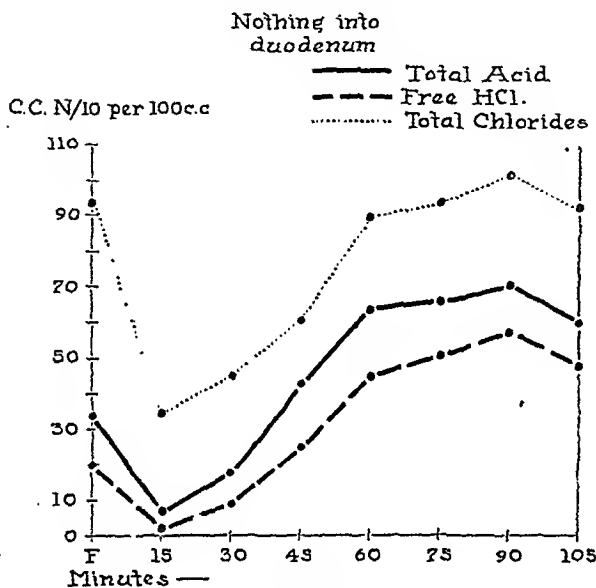


which we hope to obtain data that will supply the details now lacking.

### METHOD

We studied 11 patients with a normal gastric acid response to the Ewald meal who had no demonstrable organic gastro-intestinal disease. After an overnight fast, the patient was intubated with two Rehfuß tubes. The tip of one was allowed to pass into the duodenum by the usual technique while the other re-

#### Or.- Ewald Meal by mouth



mained in the stomach, in the usual position for gastric analysis. The length of this gastric tube, from tooth mark to tip, was kept constant for each subject throughout the course of the experiments in order to assure intubation at the same gastric level. Where the duodenum was intubated, the position of the tubes was determined fluoroscopically. The fasting gastric contents were removed and the test meal was administered by mouth. The test meal consisted of 30 gms. of zweiback and 300 cc. of distilled water at body temperature. Duodenal instillation of the glucose solution was begun with the mouth meal. Blood sugar determinations were done at half hour intervals throughout the experimental period, and 10 cc. fractions of the gastric contents were removed at 15-minute intervals until the stomach was empty. We also studied the effects of hyperglycemia produced by intravenous glucose drip using 10% solutions. Higher concentrations of glucose were avoided to prevent too extensive osmotic effect from stronger solutions reported by Day and Komarov (4).

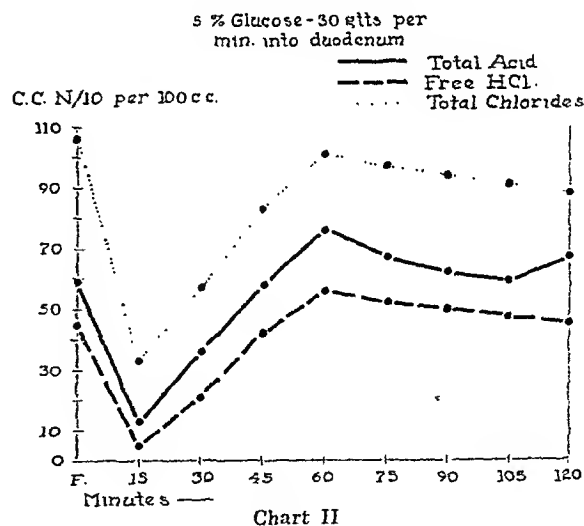
### EFFECT OF GLUCOSE IN THE DUODENUM UPON GASTRIC SECRETION

The charts employed are illustrative of the results uniformly obtained. All experiments in which duodenal regurgitation occurred as evidenced by bile staining of one or more of the gastric specimens were discarded.

Chart I shows the gastric secretory result obtained with our test meal in patient Or., when nothing was

instilled through the tube into the duodenum. Chart II represents the results obtained in the same patient after a similar test meal when 5% glucose was instilled into the duodenum at the rate of 30 drops per minute. Chart III shows the results at another test period under similar experimental conditions except that 27% glucose was substituted for the 5% solution. The data show that the 5% glucose, a relatively isotonic solution, when instilled into the duodenum produced no significant effect upon either gastric emptying or the curve of gastric acidity. The duodenal instillation of hypertonic glucose solution had a striking effect upon both gastric emptying and the gastric secretory curve. In a previous report (5), we have shown that the effect of hypertonic glucose solutions in the duodenum upon gastric motility was dependent upon the stimulation of the duodenal mucosa resulting from the change in osmotic pressure produced. The isotonic solution, not materially altering osmotic conditions in the duodenum, failed to alter gastric motility. The gastric secretory curve responds in a similar manner: the isotonic solution producing no significant change, if at all, while the hypertonic solution produces a marked depression of secretion a result like that seen after the duodenal instillation of fats, fatty acid and soap solutions (6). The effect of other agents when instilled into the duodenum is to produce gastric secretory depression, which may be considered a result of their local action upon the duodenal mucosa. A similar effect, alone resulting from glucose instillation cannot be assumed. This, because

#### Or.- Ewald Meal by mouth



the relationship of blood sugar levels to gastric secretion must be considered.

The study of the effect of glucose solutions in the intestine upon gastric secretion has not been neglected. As a matter of fact, Aldor (7) in 1900, in human subjects, reported an increase of volume and a decrease in acidity and pepsin after a test meal plus 60 gms. of glucose given by mouth, as compared with the test meal alone, and Clemm (8) in 1901 found a marked lessening of secretion in the Pavlov pouch of dogs after adding 20% dextrose to a milk meal.

In 1900, Leconte (9) working with gastric and duodenal fistula dogs found that the duodenal injection of only 10 cc. of 25% glucose was capable of producing gastric secretory inhibition. Matsuyama (10) in similarly prepared animals, using milk as the test meal, found that the duodenal introduction of hypertonic glucose had a depressant effect upon gastric secretion, if secretion was active at the time, or an inhibiting effect after the test meal if no active gastric secretion were underway when the glucose was intro-

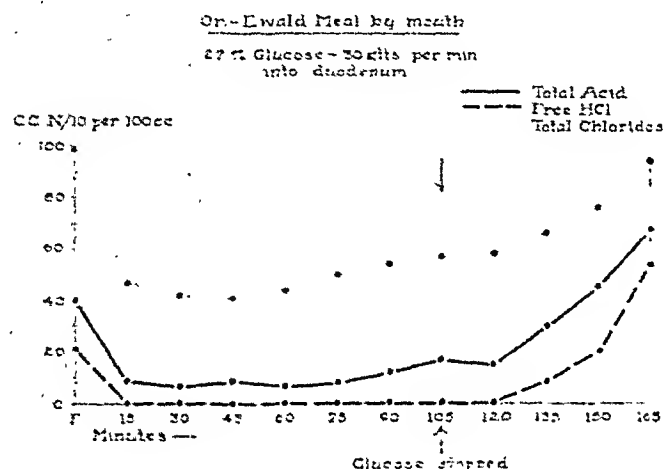


Chart III

duced. More recently, Day and Komarov (4) studied this problem in dogs. In addition to showing that the intraduodenal administration of hypertonic glucose diminished gastric secretion, they found in dogs with glucose what we have reported for man after the duodenal instillation of fats; (6) namely, that the cephalic phase of gastric secretion is especially influenced by the duodenal mechanism. Thus a 40% glucose solution introduced into the duodenum resulted in complete inhibition of gastric secretion after sham feeding. However, even after more concentrated solutions of glucose, there was only a slight inhibition of the gastric response to the injection of histamine. Matsuyama (10), too, had found that glucose introduced into the small intestine of dogs prevented a secretory response to a milk meal for as long as two hours in some cases, but failed to prevent active secretion after histamine injection.

In man, Kauders and Porges (11) using a single tube technic, found that highly concentrated dextrose solutions instilled into the duodenum produced a marked inhibitory effect upon gastric secretion. Gutzeit (12) reported a similar response when using a caffeine test meal and Matsuyama (10) with Ewald or rice-gruel meals found gastric acidity to be particularly low for 45 to 60 minutes after ingestion of the meal when hypertonic glucose was introduced into the small intestine. On the other hand, Okada et al (13) found an initial increase of gastric secretion in human subjects in the first 15 to 30 minutes after the injection of a 25% glucose solution into the jejunum.

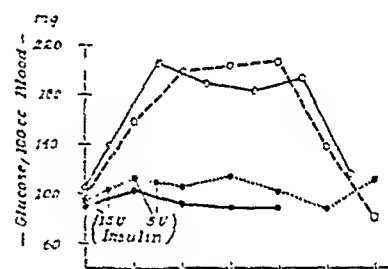
While the results in both man and dog are practically in agreement that the duodenal introduction of hypertonic glucose will diminish gastric secretion, agreement is not so universal as to the mechanism involved in the depression, when the part played by an increased blood sugar is considered.

Okada and his associates (13) were of the opinion that it was the hyperglycemia which was responsible for the gastric secretory depression. Roholm (14), however, after the injection of adrenalin found no significant change in gastric secretion during the resultant hyperglycemia. Kalk and Meyer (15) could demonstrate no constant effect of intravenous dextrose (up to 20 gms.) or of adrenalin in the hyperglycemic phase either upon the amount of gastric secretion or upon acidity of the fasting stomach. In experiments on gastric fistula dogs, they found that the acidity and amount of secretion obtained after meat ingestion could not be changed by the intravenous administration of dextrose. Day and Komarov (4) in their experiments involving the intraduodenal instillation of hypertonic glucose found by estimating the blood sugar immediately before the experiment and two minutes after the administration of glucose was completed, that the glucose was absorbed very rapidly from the intestine, but that the inhibitory effect on gastric secretion was noticeable long before the development of hyperglycemia.

In our experiments in man we have attempted to separate the local duodenal factor activated by the hypertonic glucose and the resultant hyperglycemia as they relate to this problem. In order to do so, we first established the effect of the intraduodenal instillation

ST-WC (HCF 100)

# BLOOD GLUCOSE



# FREE ACID

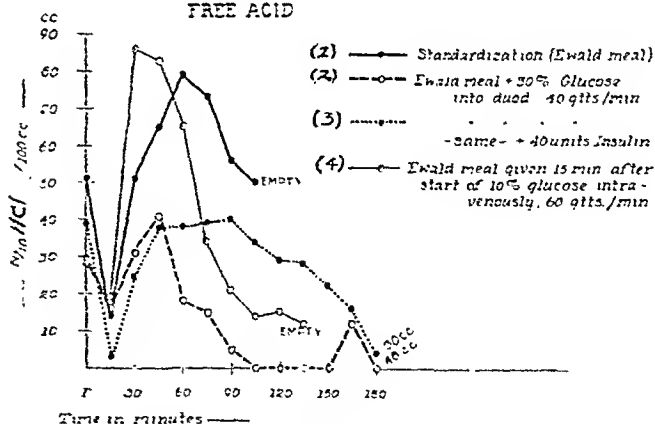


Chart IV

of 30% glucose upon the response to the gastric test meal. Blood sugars were taken fasting and at half-hour intervals throughout the test period (Chart IV, Curve 2). When these were obtained, the tests were repeated and varying doses of insulin injected at different periods until a combination was obtained in which a blood-sugar rise was prevented throughout the test period while the 30% glucose was instilled into the duodenum (Chart IV, Curve 3). Several

trials on each patient were necessary before the proper timing and dosage of insulin were obtained. Chart IV illustrates the results. Curves 1 represent the free acid curve and the half-hour blood-sugar determinations after our gastric test meal when nothing was instilled into the duodenum. Curves 2 show the respective responses after the duodenal instillation of 30% glucose at the rate of 40 drops per minute starting with the ingestion of the meal and continued throughout the test period. One sees the striking depression of gastric acidity, the increased gastric emptying time, as well as the hyperglycemia. The stomach instead of being empty at 105 minutes (Curve 1) still had 48 cc. at 180 minutes. This is, of course, in keeping with the effect upon gastric evacuation of the hypertonic glucose in the duodenum.

The decreased gastric acidity may, however, be the result of both duodenal stimulation and elevated blood sugar. Curves 3 were the results obtained when insulin injections were so staggered with the duodenal instillation of the 30% glucose that no rise in blood sugar occurred. One sees under these conditions the curve of gastric acidity to be somewhat different from that of Curve 2 although there is no significant difference in the rates of gastric evacuation. Thus during the first 45 minutes, the cephalic phase of gastric secretion appears to be equally depressed in both Curves 2 and 3. In Curve 2, when the blood sugar level had reached hyperglycemic levels, further depression of gastric acidity occurred. In Curve 3, when these hyperglycemic levels were prevented by insulin, the additional depression of gastric acidity did not appear, so that the succeeding portion of the acid curve is at a higher level than that of Curve 2. From results such as these, it appears that the depression of gastric secretion by the duodenal instillation of hypertonic glucose is the result mainly of the duodenal stimulation resulting from the osmotic changes produced by the hypertonicity of the glucose solution and is relatively little dependent upon the hyperglycemia. This we believe justified, because depression of acidity was evident before hyperglycemic levels were reached and therefore dependent entirely upon the changed osmotic conditions in the duodenum. The latter findings are similar to those previously reported by Day and Komarov (4). We hope to define this phase of the problem more clearly as it concerns man, with our improved experimental method.

We also studied the effects of hyperglycemia produced by intravenous glucose. We limited ourselves to 10% glucose given at a relatively slow rate in order to minimize changes in the osmotic concentration of the body fluids such as were reported by Day and Komarov (4) in their dogs after highly concentrated glucose injections. We hoped thus to be able to study the effect upon gastric acidity produced by hyperglycemia alone. Curves 4 illustrate the results obtained. The 10% glucose was instilled intravenously at the rate of 60 drops per minute and started 15 minutes before the test meal was given. Coincidentally a blood sugar curve was produced which was virtually identical with

that obtained in Curve 2 after the duodenal instillation of the 30% glucose.

Comparing gastric acid Curve 4 with that of Curve 1, one sees a sharper rise in gastric acidity in Curve 4, during which period a definite hyperglycemia had not yet been established. This sharp rise might be an expression of the gastric secretory stimulation reported by Friedman (20) as an immediate effect of glucose injection. When hyperglycemia is established a sharper drop in acidity occurs and an appreciably lower level of acidity is reached at the period corresponding to the time of gastric emptying in Curve 1. This again illustrates that although hyperglycemia does not produce the striking reduction of gastric acidity which follows the duodenal instillation of hypertonic glucose solution, it does appear to cause some depression. Matsuyama (16) reported that the injection of 12 to 15 gms. of glucose (25%) intravenously caused a reduction of the gastric secretory response to Ewald and rice-gruel meals. He believed the reduction was due to the hyperglycemia and not to osmotic effects, because he saw no depression of secretion after the injection of a 4.25% salt solution, a solution osmotically similar to a 25% glucose solution. This explanation, however, may not be adequate since the excretion of the glucose may involve a chloride shift sufficient to modify gastric secretion, while such a shift would not result from the injection of the hypertonic salt solution.

In dogs with gastric and oesophageal fistulae, Matsuyama (17) found that the subcutaneous injection of glucose before mock feeding prevented gastric secretion almost entirely, although he was unable to obtain any effect whatever upon the secretion produced by histamine and gastrin.

Although our results to date would indicate only a moderate effect upon gastric secretion by hyperglycemia, such prolonged or repeated results as could occur in the diabetic may well explain the higher-than-average incidence of anacidity in diabetes. Thus while Okada, Aoyama and Sugita (18) found that hyperglycemia excited an inhibitory effect on the secretory nerve centers and that the inhibition was transmitted by way of the parasympathetic nervous system, the stimulus had to be of a certain degree and duration to produce an effect. Furthermore, it has been shown (19) that anacidity developed usually in the diabetic of long standing.

#### SUMMARY

With a two tube technique in man, the influence of glucose solutions instilled intraduodenally and intravenously upon the response of the stomach to test meals was investigated. An attempt was made to separate the duodenal effect upon gastric acidity resulting from the osmotic changes produced by hypertonic glucose and the possible effect of the resultant hyperglycemia. Our evidence at present indicates the most striking effect to be dependent upon the altered osmotic conditions in the duodenum, while the hyperglycemia plays only a secondary role. The latter, however, may be sufficient to explain the higher-than-average incidence of anacidity in diabetes.

#### REFERENCES

1. Babkin, B. P.: The Triple Mechanism of the Chemical Phase of Gastric Secretion. *Am. J. Dig. Dis.*, 5:467, 1938.
2. Bowen, B. D. and Aaron, A. H.: Gastric Secretion in Diabetes Mellitus. *Arch. Int. Med.*, 37:874, 1926.
3. Rothenberg, R. E. and Teicher, L.: Diabetes Mellitus and Peptic Ulcer. *Am. J. Dig. Dis. and Nutrit.*, 5:663, 1928.
4. Day, J. J. and Komarov, S. A.: Glucose and Gastric Secretion. *Am. J. Dig. Dis.*, 6:169, 1939.
5. Gershon-Cohen, J., Shay, H. and Fels, S. S.: Experimental Studies on Gastric Physiology in Man: Influence of Osmotic Pressure.

- Changes of Salt and Sugar Solutions on Pyloric Action and Gastric Emptying in Normal and Operated Stomach. *Am. J. Roent.*, 40:335, 1938.
6. Shay, H. Gershon-Cohen, J. and Fels, S. S.: The Role of the Upper Small Intestine in the Control of Gastric Secretion; the Effect of Neutral Fat, Fatty Acid and Soaps. *Ann. Int. Med.*, 13:294, 1939.
  7. Aldor, L.: Ueber die Künstliche Beeinflussung der Magensekretion. *Ztschr. f. klin. Med.*, 40:248, 1900.
  8. Clemm, W. N.: Ueber die Beeinflussung der Magensaftabscheidung durch. *Zucker. Therap. Monatshefte.*, 15:403, 1901.
  9. Le Conte, P.: Fontions Gastro-Intestinales. *La Cellule.* 17:285, 1900.
  10. Matsuyama, M.: Influence of the Introduction of Glucose Into the Intestine Upon the Secretion of the Gastric Juice. *Jap. J. Gastro-Enterol.*, 4:273, 1932.
  11. Kauders, F. and Porges, O.: Der Einfluss des Duodenalinhalt auf die Magensekretion. *Wien. klin. Wchnschr.*, 35:838, 1922.
  12. Gutzeit, E.: Ueber die Beeinflussung der Magenreiz und Nuchtern Sekretion durch Duendarmverweilsonden sowie durch duodenale und jejunale Nahrungszufuhr. *Zeit. f. d. Gesam. Exp. Med.*, 73:48, 1930.
  13. Okada, S., Kuramochi, K., Tsukahara, T. and Ooinoue, T.: Pancreatic Function IV. The Humoneuronal Regulation of the Gastric, Pancreatic and Biliary Secretions. *Arch. Int. Med.*, 43:446, 1929.
  14. Roholm, K.: Clinical Investigation Into the Effects of Intravenous Injection of Insulin. *Acta. Med. Scand.*, 73:472, 1930.
  15. Kalk, H. and Meyer, P. F.: Blutzuckerspiegel und Magensekretion. *Zeitschr. f. klin. Med.*, 120:692, 1932.
  16. Matsuyama, M.: Influence of the Intravenous and Subcutaneous Administration of Glucose on the Secretion of the Gastric Juice. *Jap. J. Gastro-Enterol.*, 5:37, 1933.
  17. Matsuyama, M.: The Behavior of Sugar Towards the Secretion of the Gastric Juice. *Jap. J. Gastro-Enterol.*, 4:262, 1932.
  18. Okada, S., Aoyama, S. and Sugita, A.: Blutzuckerspiegel und Magentaetigkeit. *Ztsch. f. Klin. Med.*, 127:89, 1934.
  19. Wohl, M. G.: Diabetes Mellitus and Gastric Secretion. *J. Lab. and Clin. Med.*, 17:22, 1931.
  20. Friedman, M. H. F.: The Influence of Glucose Administration on Gastric Secretion. *Am. J. Physiol.*, 126:495, 1939.

## The Relationship Between Gastric Acidity and Calcium\*

By

FRANK C. VAL DEZ, M.D.†

and

JULIUS SENDROY, JR., Ph.D.

CHICAGO, ILLINOIS

CALCIUM has been of interest in the physiology of gastric secretion from two standpoints: (a) the effect on gastric secretion and acidity, of changes in the usually constant, normal, serum calcium level; and (b) the factors governing the calcium content of gastric juice itself.

The former problem has been studied mainly by the experimental production of hypocalcemia by parathyroidectomy and the injection of phosphates, and of hypercalcemia by the injection or administration of calcium salts, parathormone, or ergosterol. The relatively few studies in the literature show practically complete agreement to the effect that hypocalcemia results in, or is accompanied by, diminished gastric secretion and acidity. With respect to hypercalcemia, the results of which have been much more extensively studied, there is less unanimity, although the majority of workers have observed the same effect in this condition also, namely, an inhibited gastric secretory response. Babkin (1, 2) has presented the most recent exposition of these problems.

The concentration of calcium in gastric juice itself, and the factors causing variations in the values have received much less attention. There is a wide range of apparently normal fasting or histamine stimulated values, from those of Rosemann (3), of 0.04 to 0.11 mE. per liter for dogs, to those of Rudd (4), of 2.0 to 4.3 mE. per liter for humans (5-8). Results of the effects of hypo- or hypercalcemia on gastric juice calcium are equivocal (9-11), although the most recent work by Grant (12) has shown elevated values after injection of calcium salts. A partial explanation for the present widely divergent results may be made on the basis of observations of Rudd (4), of Kirsner and Bryant (7), and of Grant (13), that there is a reciprocal relationship between calcium and acidity in gastric juice. Further, Grant (14) has shown that mucus can be a ready source of gastric calcium. Obvi-

ously, the adequate control of the above factors should afford a more intelligent interpretation of gastric secretion studies, and a better understanding of the underlying physiology.

It was the purpose of the present work to shed further light on the above questions, by the use of certain refinements in experimental technique and analysis, in studies of the gastric secretion of human beings. An attempt was made to study the effect of hypercalcemia on gastric function in normal subjects by the use of a relatively new substance, dihydrotachysterol, known to be specific for blood calcium elevation in hypocalcemia. Although our expectations were not fulfilled in this direction, the results obtained do provide further evidence in support of a reasonable explanation for the presence of calcium in gastric juice, in the concentrations found by various workers.

### METHODS

The subjects were eight male students in their early twenties, presumably normal and with gastric function unimpaired. After withdrawal of a blood sample, a Sawyer tube was inserted, and the fasting stomach emptied of its contents. Following the injection of 0.5 mgm. of histamine phosphate, accumulated stomach juice was completely withdrawn at 15 minute intervals, over a period of 1¾ hours. During this period, provision was made to avoid the swallowing of saliva by the subject. There then followed a period of several days, during which the administration of capsules of dihydrotachysterol, in the doses indicated in Table I, was controlled by serum calcium analyses, and Sulko-witch (15) tests of the urine. The period was terminated by a repetition of the determination of the gastric secretory response to histamine, as outlined above.

Upon withdrawal, each sample of gastric juice was measured for volume and immediately centrifuged (for 5 minutes at 2500 r.p.m.). The supernatant fluid was separated from solids or mucus present (the volume of which was noted), without delay. Analyses.

\*From the Department of Experimental Medicine, Loyola University School of Medicine, and Mercy Hospital.

Read at the Annual Session of the American Gastro-Enterological Association at Atlantic City, June 8-9, 1942.

†Department of Medicine.

were then carried out on the individual samples as follows: Acidities, to pH 3.5 with brom phenol blue, and to pH 7.0 with phenol red (Hollander (16)) were determined by microtitration with 0.05 N NaOH, of 1.0 cc. (or 0.5 cc.) samples. The modified MacInnes and Belcher (17) electrode used by Sendroy, Shedlovsky and Belcher (18) was used with a cathode ray electron tube (GE5) potentiometer, for the measurement of pH at 38° C. The values obtained with this instrument, standardized against 0.1 N HCl, the pH of which was assumed to be 1.08, have been found accurate within 0.01-0.02 pH. Calcium, in 0.5 cc. samples of gastric juice and in 0.2 cc. samples of serum (both diluted to about 1.5 cc.) was precipitated

Table 1  
Results of Fractional Absorption of Gastric Acid, and of Serum Calcium

| Subject | Sex | Age | Dose of Dihydrocholesterol (mg.) | Time (min.) | pH (mmole/liter) at minute intervals shown |      |      |      |      |      |      |      |      |      | Vol (cc.) | Ca (mg/100 cc.) |
|---------|-----|-----|----------------------------------|-------------|--|------|------|------|------|------|------|------|------|------|-----------|-----------------|
|         |     |     |                                  |             | 0  | 15   | 30   | 45   | 60   | 75   | 90   | 105  | 120  |      |           |                 |
| 1       | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 2       | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 3       | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 4       | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 5       | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 6       | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 7       | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 8       | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 9       | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 10      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 11      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 12      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 13      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 14      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 15      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 16      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 17      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 18      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 19      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 20      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 21      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 22      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 23      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 24      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 25      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 26      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 27      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 28      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 29      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 30      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 31      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 32      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 33      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 34      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 35      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 36      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 37      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 38      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 39      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 40      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 41      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 42      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 43      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 44      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 45      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 46      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 47      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 48      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 49      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 50      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 51      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 52      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 53      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 54      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 55      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 56      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 57      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 58      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 59      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 60      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 61      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 62      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 63      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 64      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 65      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 66      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 67      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 68      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 69      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 70      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 71      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 72      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 73      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 74      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 75      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 76      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 77      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 78      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 79      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 80      | M   | 34  | 100                              | 0           | 1.44                                       | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44 | 1.44      | 1.44            |
| 81      | M   | 34  | 100                              | 0           |  |      |      |      |      |      |      |      |      |      |           |                 |

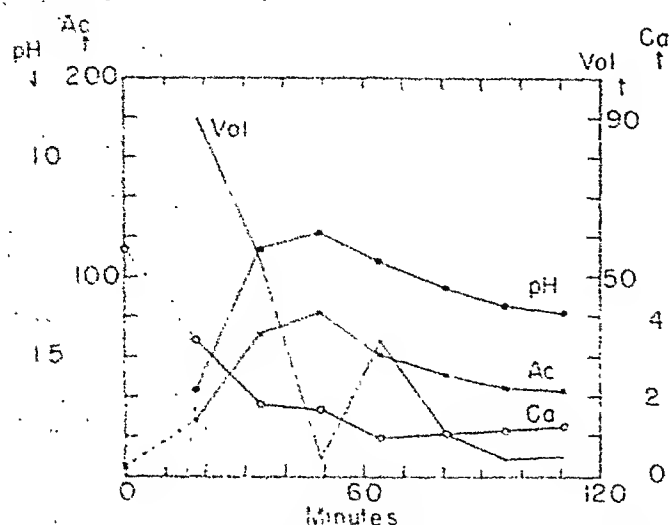


Fig. 3. Curves (Mi-1) for gastric secretion obtained when levels of pH and calcium in fasting juice are high.

vomiting, anorexia and exanthems exhibited by three of the subjects. Of these, only W yielded a serum calcium value definitely higher than normal. Evidently, in spite of the increased calcium available (presumably because of increased absorption) resulting from dihydrotachysterol administration, we have found it difficult, with this drug, in these normal cases, to increase the blood calcium for any length of time. The urinary threshold mechanism promptly disposes of the excess, at least, during the periods covered in our study. The hypercalcemic effect of dihydrotachysterol is known to be prolonged, and further investigation may reveal a greater lag in its effect on normals than on hypocalcemic individuals.

Comparison of the data covering the first and second secretion curves of each individual (before and after dihydrotachysterol), shows, in the one case of definitely increased serum calcium (W, 2), a definitely decreased pH; and in the second experiment on the other subjects, a slight, general, similar tendency. In hypercalcemia, as indicated above, on the basis of the work of others, an inhibited gastric acidity would be expected. Until this question is investigated further, with the production of hypercalcemia in a larger group of subjects, definite conclusions as to the general effect of dihydrotachysterol on gastric secretion, on the basis of these results, does not seem to be warranted.

**Calcium in Gastric Juice.** Although the results are in accord with the principle that pH and calcium change in the same direction and independently of the volume output (13), they show a tendency towards decreased gastric juice calcium concentration after dihydrotachysterol, at a time when excess calcium is being excreted in the urine. In hypercalcemia associated with a decreased acidity, an increased gastric calcium would be expected. Evidently, the factor governing the gastric calcium level is primarily associated with the acidity of the gastric juice, and not with the serum calcium level.

The most interesting features of our results, however, are (1) that these clinical gastric secretion curves of humans are consistent with various phases of animal experimentation by others, and (2) that they lend still greater support to an explanation of the

role of gastric acidity as a factor in determining the level of calcium in gastric juice. The following considerations will provide a proper background for a more critical evaluation of these data.

Under the conditions of our experiments, the composition of the individual samples aspirated from the stomach will depend on the following factors: (1) the relative volumes or rate of secretion (8) of the different components, acid and non-acid (20), or parietal and non-parietal, mucous fluid, etc., secreted by the various cells of the gastric mucosa, (2) the extent of contamination by, or mixture with, other fluids, duodenal fluid, bile, blood and saliva, and (3) the extent to which the secretion of each successive period may be diluted with that of the previous period, by reason of failure to secure complete emptying of the stomach with each withdrawal.

With respect to factor (1), Gray and Bucher (8) report no calcium in the parietal secretion of dogs, with 3.7 mE. per liter in the non-parietal (minimum, 0.2 mE. per liter) juice. Grant (14) has shown that HCl can take up (with simultaneous loss of acidity) considerable amounts of calcium from mucus, of as much as 2.37 (average 1.17) mE. per liter over a period of 15 minutes. These results were confirmed *in vitro* and by an observed loss of calcium from mucus exposed to HCl. Factor (2) is of importance in that the calcium content of each of the contaminating fluids mentioned above is known to be higher than that of mixed gastric juice obtained from the stomach. Factor (3) may not always be easily controlled and is therefore a considerable handicap in human clinical work as compared with animal experimentation. Under these conditions, after histamine, it would be expected that our samples of gastric juice, certainly at the height of secretion, would be composed largely of a highly acid, low calcium, parietal secretion, the calcium content of the sample being increased only to the extent of mixture with other calcium-containing fluids. Furthermore, the extra precaution of promptly separating the clear juice from the mucus would serve to eliminate the possible *in vitro* uptake of calcium which Grant has demonstrated, and which has probably been more or less a source of error in all gastric

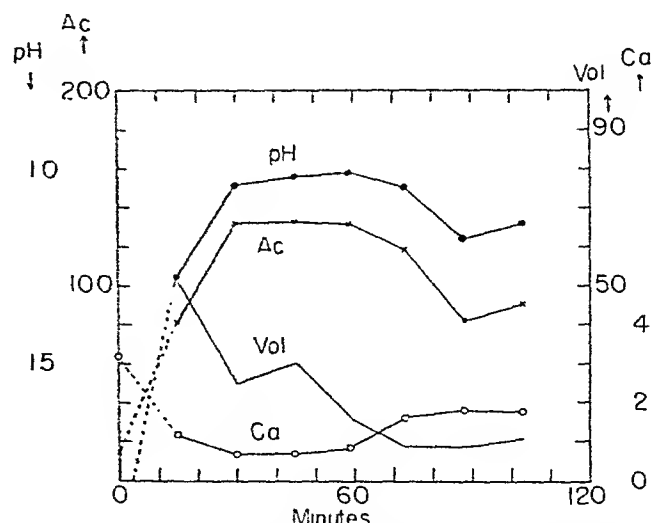


Fig. 4. Curves (Ma-1) for gastric secretion illustrating the effect of large amounts of mucus on relatively small volumes of terminal samples of juice.



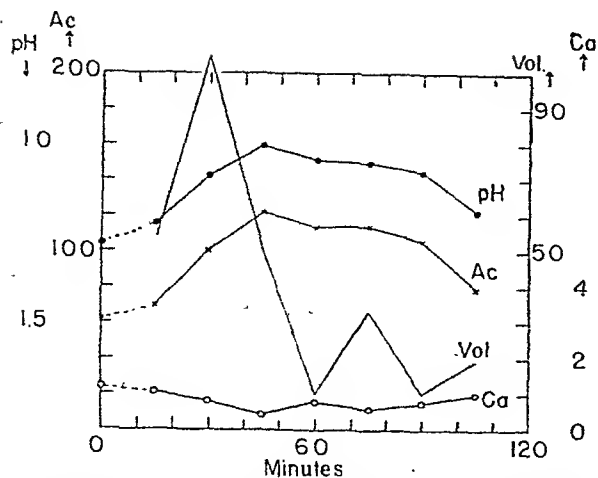


Fig. 5. Curves (*Di-1*) for gastric secretion illustrating acidity and calcium values independent of extremely high output volume.

juice calcium analyses heretofore reported in the literature.

An analysis of the curves of Table I permits the following generalizations: (1) The typical excretion curve for gastric calcium is that of *Wi-2* (Fig. 1) almost identical with that of *Wi-1*. The calcium level of the fasting sample (factor 3) affects and determines, largely by dilution, the calcium found in the first two samples after histamine stimulation. At the height of parietal secretion and acid production (factor 1) (45-60 minutes), the trough of minimum calcium (average 0.5 mE. per liter) is reached, following which the calcium slowly rises as the acidity decreases, and non-parietal (factors (1) and (2)) fluids enter the picture.

Apparent exceptions to or deviations from this normal type of gastric secretion curve are readily accounted for by the data of Table I (note presence of blood, bile and mucus), and are in accord with the considerations outlined above. Thus, *Hu-1* (Fig. 2) illustrates the effect of delay in centrifuging the samples and separating the clear fluid from solids and mucus (two hours after withdrawal). The high calcium (and the decreased acidity) values obtained in this case were undoubtedly the result of calcium uptake from mucus. Values higher than 1 mE. per liter at either end of the curves are usually encountered when the fasting value is high (*Mi-1*) (Fig. 3) or when there is contamination by other fluids, of relatively small volumes of gastric secretion (*MI-1*); (*Ma-1*) (Fig. 4). Comparison of *Di-1* (Fig. 5) with *Wi-2* (Fig. 1), and other fairly typical curves of the series illustrates the independence from extreme variations in volume output, of gastric juice acidity and calcium. Indeed, with the exception of the curves for volume output, Figs. 1 and 5 may be superimposed.

Fig. 6, in which the values for all the points in Table I are plotted, indicates a definite relationship between gastric juice pH and calcium. Data from Kirsner and Bryant (7) for analyses of what they describe as "mixed" "individual" samples, are also included. The preponderance of strongly acid values among our data is probably owing in no small measure, to the precaution against reaction with

mucus. The greater acidity of the majority of our samples accounts for the low calcium values, corresponding to the lowest reported in the literature (3, 8).

Although we have not essayed to draw an average curve for these results, it is apparent that such a line, if extrapolated to pH 0.85, would indicate no calcium at all in the pure parietal secretion of 0.17 N HCl (14, 15). With the exception of the high-calcium points for *Ma-1* and *MI-1* mentioned above, all points, even those for fasting, clearly indicate the pH-calcium relationship, which is merely an index of the extent to which the parietal HCl secretion containing practically no calcium, is diluted with other non-parietal, calcium-containing fluids.

### SUMMARY

The direct relationship of calcium to pH in gastric juice has been confirmed in a study of 15 gastric secretion curves, after histamine, of 8 normal human individuals. The results indicate that (a) gastric calcium is lowest at the height of acid secretion and (b) that pH as a factor governing the calcium content of gastric juice is merely a reflection of the extent to which parietal HCl secretion is diluted with non-parietal fluids or substances.

### REFERENCES

1. Babkin, B. P.: The Effect of Parathyroid Hormone and of Activated Ergosterol on Gastric Secretion in the Dog. *Rec. Gastro-Enterol.*, 7, pp. 373-382, 1940.
2. Babkin, B. P., Komarov, O. and Komarov, S. A.: The Effect of Activated Ergosterol and of Parathyroid Hormone on Gastric Secretion in the Dog. *Endocrinology*, 26, pp. 703-715, 1940.
3. Rosemann, R.: Beiträge zur Physiologie der Verdauung. 1. Die Eigenschaften und die Zusammensetzung des Durchschießflüssigkeits.

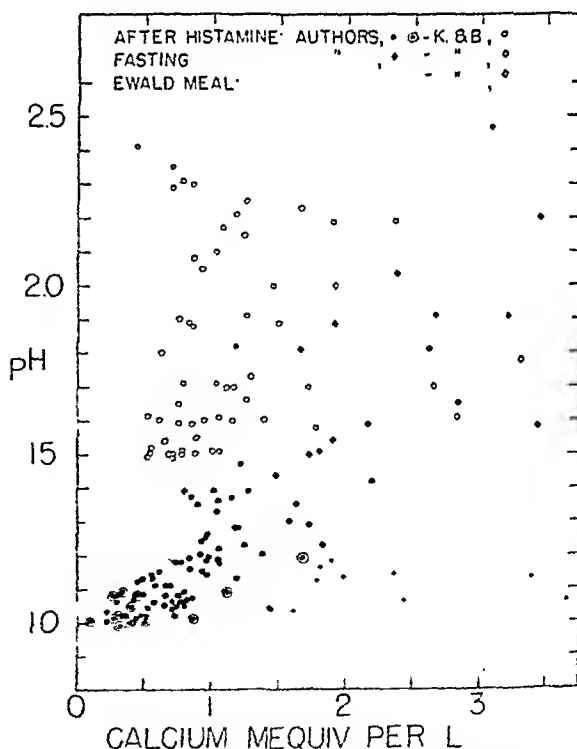


Fig. 6. The relationship between pH and calcium of gastric juice. Solid points correspond to values in Table I, hollow points to data from Kirsner and Bryant (7). The abnormal location of points marked ? is accounted for in the discussion of *Ma-1* (Fig. 4) and *MI-1* in the text. Values for curves at the height of secretion are ringed.

lerung gewonnen Hundemagensaftes. *Pflüger's Archiv. für die gesammte Physiologie*, 118, p. 467, 1907.

4. Rudd, G. V.: Studies on the Composition of the Gastric Juice. *Med. J. Australia*, 21, pp. 431-436, 1934.
5. Gamble, J. L. and Melver, M. A.: The Acid-Base Composition of Gastric Secretion. *J. Exper. Med.*, 48, pp. 837, 1928.
6. Bonne, C., Hartz, P. H., Klerks, J. V., Posthuma, J. H., Radema, W. and Tiokronogoro, S.: Morphology of the Stomach and Gastric Secretion in Malays and Chinese and the Different Incidence of Gastric Ulcer and Cancer in These Races. *Am. J. Cancer*, 33, p. 265, 1938.
7. Kirsner, J. B. and Bryant, J. E.: The Calcium Content of Gastric Juice. *Am. J. Dig. Dis.*, 6, pp. 704-708, 1939.
8. Gray, J. S. and Bucher, G. R.: The Composition of Gastric Juice as a Function of the Rate of Secretion. *Am. J. Physiol.*, 133, pp. 542-550, 1941.
9. Austin, W. C.: The Effect of the Parathyroid Hormone on Gastric Secretion. The Calcium Content of Gastric Juice. *J. Biol. Chem.*, 74, Proc. (XXI), p. ixix, 1927.
10. Austin, W. C. and Matthews, S. A.: I. The Effect of the Parathyroid Hormone on Gastric Secretion. II. The Calcium Content of Gastric Juice. *Am. J. Physiol.*, 81, pp. 532-559, 1927.
11. Farbes, C. I. and Cahane, M.: Sur l'Acidité et la Teneur en Calcium du Suc Gastrique Chez les Animaux Thyro-parathyroïdectomisés ou Traités par la Parathormone. *Compt. rend. soc. Biol.*, 100, pp. 243-245, 1932.
12. Grant, R.: The Inhibition of Gastric Secretion by the Intravenous Injection of Calcium Salts. *Am. J. Physiol.*, 132, pp. 470-468, 1941.
13. Grant, R.: The Relation of Calcium Content to Acidity and Buffer Value of Gastric Secretions. *Am. J. Physiol.*, 132, pp. 457-473, 1941.
14. Grant, R.: Calcium in Gastric Mucus and Regulation of Gastric Acidity. *Am. J. Physiol.*, 133, pp. 494-503, 1942.
15. Albright, F.: Note on the Management of Hypoparathyroidism with Dihydrocholesterol. *J. A. M. A.*, 112, pp. 2582-2593, 1935.

16. Hollander, F.: Studies in Gastric Secretion. II. A Comparison of Criteria of Acidity Used in This Investigation. *J. Biol. Chem.*, 91, pp. 481-492, 1931.
17. MacInnes, D. A. and Belcher, D.: A Durable Glass Electrode. *Ind. and Eng. Chem., Anal. Ed.*, 5, p. 199-200, 1933.
18. Sendroy, J., Jr., Shedlovsky, T. and Belcher, D.: The Validity of Determinations of the pH of Whole Blood at Thirty-eight Degrees with the Glass Electrode. *J. Biol. Chem.*, 115, pp. 529-532, 1936.
19. Sendroy, J., Jr.: Photoelectric Determination of Oxalic Acid and Calcium, and Its Application to Micro- and Ultramicroanalysis of Serum. *J. Biol. Chem.*, 144, pp. 243-258, 1942.
20. Hollander, F.: The Components of the Gastric Secretion. *Am. J. Dig. Dis. and Nutrit.*, 3, pp. 651-655, 1936.
21. Hollander, F. and Cowgill, G. R.: Studies in Gastric Secretion. I. Gastric Juice of Constant Acidity. *J. Biol. Chem.*, 91, pp. 151-182, 1931.
22. Hollander, F.: Factors Which Reduce Gastric Acidity. *Am. J. Dig. Dis.*, 5, pp. 364-372, 1935-1939.

## DISCUSSION

DR. JOSEPH B. KIRSNER (Chicago): I merely wish to confirm the observations of Drs. Val Dez and Sendroy.

In 1939 I performed a similar study using a rather large series of patients, including those with and without gastric disease, and observed, as they have, a definite relationship between the calcium content of gastric juice and the gastric acidity. Namely, the greater the hydrogen ion concentration, the lower the calcium content of gastric juice.

# The Acid Factor in Duodenal Ulcer as Evaluated by the Acidity and Neutralizing Ability in the Duodenal Bulb\*†

By

J. EDWARD BERK, M.D., M.Sc. (Med.)‡ J. EARL THOMAS, M.D.

and

MARTIN E. REHFUSS, M.D.

PHILADELPHIA, PENNSYLVANIA

THE vast work dealing with the acid factor in duodenal ulcer has been concerned almost exclusively with the acidity in the stomach. Much is assumed but no body of precise knowledge is available concerning the acidity in the region of the duodenum where most clinical ulcers are found (5, 7). The relationship between the acidity in the stomach and that in the ulcer-bearing duodenal bulb is particularly in need of further investigation (7). This study was undertaken primarily to supply some knowledge of the reaction and neutralizing ability of the contents of the first part ("ulcer-bearing area") of the duodenum under various conditions of gastric acidity in order that the acid factor in duodenal ulcer might be evaluated more rationally. The results which are summarized in this presentation have been (1, 2) or will be published in detail.

## METHODS

Studies of gastric and duodenal acidity were made on 7 dogs, 22 normal human subjects, and 23 patients with duodenal ulcer. Samples of gastric and duodenal contents were simultaneously collected from areas just above (pars pylorica) and just below (duodenal bulb) the pylorus. In the dogs appropriate collecting tubes

were inserted through cannulated gastric and duodenal fistulas (8, 12). In the humans a specially constructed double lumen tube was used whose position was controlled fluoroscopically during the course of the experiment and then proven at the end of the period of observation by means of roentgenograms taken before and after the introduction of barium directly into the duodenal cap (1).

All the subjects were studied in the fasting state and after an Ewald meal. The dogs, in addition, were studied following meals consisting respectively of 500 cc. of cream (20% fat) and 500 cc. of Liebig's extract (Difco Laboratory paste preparation dissolved in distilled water) (6, 13), accompanied by the subcutaneous injection of 0.1 mg. of histamine base per 10 Kg. of body weight. The latter was intended to cause a temporary condition of gastric hypersecretion. Two groups of duodenal ulcer patients were also studied following an Ewald meal plus the administration 30 minutes after the meal of 15 cc. of aluminum hydroxide gel (Amphojel) in the one group, and a powder consisting of 0.6 gram of sodium bicarbonate and 2 grams of calcium carbonate (Sippy powder) in the other.

Free acid, total acidity and pH were determined on all the samples collected from both stomach and duodenum in all the subjects. On the duodenal samples, in addition, the amount of N/10 hydrochloric acid needed to bring about a colorimetric reaction for free acid was determined. This was called the "excess

\*From the Departments of Physiology and Medicine of The Jefferson Medical College of Philadelphia.  
†Aided by a grant from John Wyeth & Bro., Inc.  
‡Ross V. Patterson, Fellow in Gastro-Enterology.  
Abridgement of a thesis submitted by Dr. Berk to the Faculty of the Graduate School of Medicine of the University of Pennsylvania in partial fulfillment of the requirements for the degree of Doctor of Medical Science (D.Sc. (Med.)) for graduate work in internal medicine. Read at the Annual Meeting of the American Gastro-Enterological Association at Atlantic City, N. J., June 8-9, 1942.

neutralizing ability of the duodenal contents" and was expressed in clinical units.

Of the technically satisfactory experiments performed, 149 were made on the dogs, 48 on the normal human subjects, and 124 on the duodenal ulcer patients.

### RESULTS

To facilitate comparisons between the different groups under the various experimental conditions the results have been summarized in Table I. The figures given for each of the designated subjects were derived by averaging all the results obtained in each category throughout the entire period of observation. Average figures, however, mask many tendencies which were evident in the individual experiments.

There was a consistent difference in the acidity of samples collected simultaneously from just above and below the pylorus whose magnitude can be seen by a comparison of the average gastric and duodenal pH and titratable acidity values given in Table I. Not only is gastric acidity immediately reduced in the duodenal bulb, but the average values for "excess neutralizing ability" given in Table I indicate that the first part of the duodenum is equipped with a neutralizing, buffering and diluting capacity considerably in excess of its physiological needs with respect to the free acid of the gastric chyme. Nonetheless, the important "ulcer-bearing" duodenal bulb is characteristically an acid area even in normal people (Table I). Moreover, free acid in the contents of the first part of the duodenum is by no means infrequent in many normal individuals both under fasting conditions and during the course of digestion (Table II). These

findings are worth emphasizing inasmuch as they are contrary to the prevalent teaching in some quarters.

Patients with duodenal ulcer show higher average acidity values in the duodenal bulb (Table I) and a greater percentage of duodenal samples positive for free acid (Table II) than do normal people. The duodenal bulb, however, even in ulcer patients still possesses a considerable neutralizing power; the average pH is above the critical level at or below which free acid is said to be present (pH 3.5) (2c) Table I; one-half the samples do not contain free acid (Table II); a consistent difference in acidity is maintained between the contents of the pars pylorica and those of the bulb; and many samples display excess neutralizing ability (Table I).

The increase in free and total acidity in the duodenal contents of ulcer patients over the normal after an Ewald meal appears, superficially, to be inconsistent with the lack of change in excess neutralizing ability. The apparent discrepancy is due to the fact that there was, in the ulcer patients, a wider range of variation in duodenal acidity which tended to increase the average values when either the excess acidity or excess potential alkalinity "excess neutralizing ability") was considered separately. This wide range of variation is probably more indicative of impaired duodenal neutralizing function than are the averages.

Additional evidence was obtained of impaired duodenal bulb neutralization in ulcer patients. In Fig. 1 is shown a comparison of the entire group of duodenal ulcer patients with 6 normal subjects specially selected because of their high gastric acid values (3a). Of

TABLE I

*Average gastric and duodenal acidity in 7 dogs, 22 normal people and 23 patients with duodenal ulcer*

|  | pH                  |                      | Free Acid*          |                      | Total Acidity*      |                      | Excess*<br>Neutralizing<br>Ability<br>Duod. Cont. |
|--|---------------------|----------------------|---------------------|----------------------|---------------------|----------------------|---|
|  | Gastric<br>Contents | Duodenal<br>Contents | Gastric<br>Contents | Duodenal<br>Contents | Gastric<br>Contents | Duodenal<br>Contents |   |
| <i>Fasting</i>   |                     |                      |                     |                      |                     |                      |   |
| Dogs   | 1.90                | 5.56                 | 47                  | 0.6                  | 82                  | 22                   | 26  |
| Normal People  | 3.51                | 5.60                 | 15                  | 0.6                  | 38                  | 18                   | 17  |
| Duodenal Ulcer Patients  | 1.62                | 3.96                 | 31                  | 4.0                  | 58                  | 24                   | 11  |
| <i>Ewald Meal</i>  |                     |                      |                     |                      |                     |                      |   |
| Dogs   | 1.63                | 4.82                 | 40                  | 0.2                  | 93                  | 30                   | 29  |
| Normal People  | 2.78                | 4.94                 | 21                  | 1.0                  | 50                  | 24                   | 14  |
| Duodenal Ulcer Patients  | 1.68                | 3.87                 | 34                  | 7.0                  | 66                  | 33                   | 14  |
| <i>Liebig's Extract<br/>Histamine Meal</i>                                       |                     |                      |                     |                      |                     |                      |   |
| Dogs   | 2.01                | 4.54                 | 38                  | 1.0                  | 87                  | 36                   | 21  |
| <i>Cream Meal</i>  |                     |                      |                     |                      |                     |                      |   |
| Dogs   | 3.40                | 5.51                 | 6                   | 0                    | 63                  | 47                   | 38  |
| <i>Antacids* (Duodenal Ulcer<br/>Patients) (From time of<br/>admin. of ant.)</i> |                     |                      |                     |                      |                     |                      |   |
| Controls   | 1.53                | 3.71                 | 41                  | 8.0                  | 75                  | 36                   | 14  |
| Amphojel Group   | 2.25                | 3.91                 | 25                  | 6.0                  | 84                  | 37                   | 12  |
| Sippy Powder Group   | 3.02                | 4.66                 | 24                  | 4.0                  | 46                  | 21                   | 28  |

\*Expressed as clinical units (cc. of N/10 NaOH or HCl per 100 cc. contents).

TABLE II

Percentage of duodenal samples positive for free acid (pH 3.5 or less)

|                         | Fasting | Ewald Meal | Liebig's Extract—Histamine Meal | Cream Meal |
|-------------------------|---------|------------|---------------------------------|------------|
| Dogs                    | 17      | 16         | 27                              | 1          |
| Normal Human Subjects   | 26      | 52         | —                               | —          |
| Duodenal Ulcer Patients | 56      | 54         | —                               | —          |

great interest is the fact that the normal subjects, especially in the latter part of the observation period, displayed higher gastric acid concentrations and at the same time lower duodenal acid concentrations than did the patients with duodenal ulcer. Apparently, the degree of acidity of the stomach contents is not the sole determinant of the degree of acidity of the duodenal bulb contents. In duodenal ulcer patients, it is strongly suggested, there is inadequate neutralization of the gastric acid in the duodenal bulb as well as gastric hypersecretion.

The striking similarity in the average pre- and post-meal values for free and total acidity and pH in both the stomach and duodenum in the ulcer patients contrasts sharply with the lower acid values during fasting found in normal people. Apparently in the fasting state some stimulus is active in ulcer patients which is inactive in normal people.

Other factors in addition to the acidity in the stomach determine the reaction of the contents of the duodenal bulb. Chief among these contributory factors is the type of food undergoing digestion. The effect of the several basic foodstuffs on duodenal acidity is only in part dependent on the changes in gastric acidity. A comparison of the average gastric pH with the average duodenal pH following each of the three types of meals in dogs (Table I) illustrates this well. It can be seen clearly that the ratio of gastric and duodenal pH is different for the various meals and is not constant as would be the case if the one were dependent on the other.

In the dogs the failure of the Liebig's extract-his-

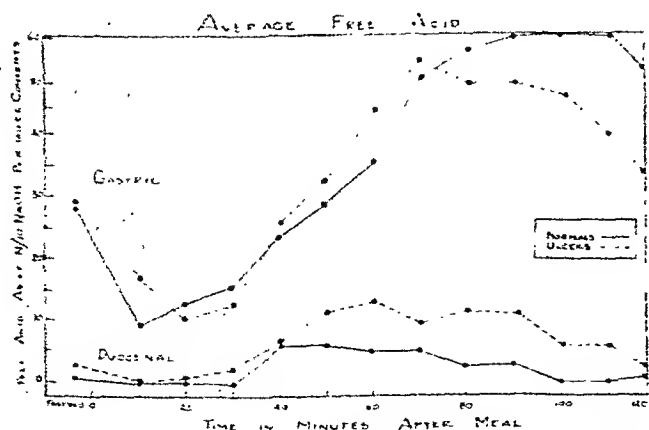


Fig. 1. Average free acid as determined on samples collected simultaneously from just above and just below the pylorus in duodenal ulcer patients compared with a group of normal subjects with gastric hyperacidity.

tamine meal to increase gastric acidity as compared with the Ewald meal was unexpected. It was probably due to the buffering and diluting effect of the meat extract and the water respectively. Rapid emptying of the liquid meal doubtless was also a factor. The ability of the dog's duodenum to accommodate the increased gastric discharge without marked increase in acidity was well demonstrated.

The higher value for duodenal total acid following the fat meal in dogs as compared with the Ewald meal in spite of the lower acid values suggested by other criteria indicates heavy buffering of the duodenal contents, probably with soaps and fatty acids.

The areas just above and below the pylorus displayed neither a close parallelism nor a constant re-

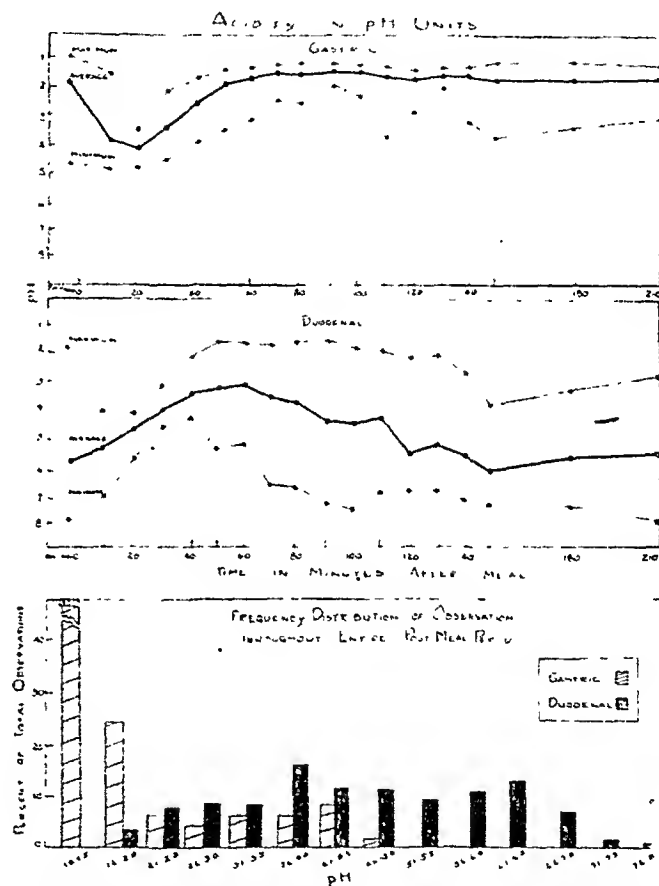


Fig. 2. Acidity in pH units of samples collected simultaneously from just above and just below the pylorus in normal dogs before and after a meal of Liebig's extract and histamine.

lationship as regards the acidity simultaneously determined in each. The discrepancy between the lines representing the plotted values of gastric and duodenal pH in dogs given a Liebig's extract-histamine meal as shown in Fig. 2 (4) is fairly characteristic of our general experience in this regard. None of the customary measures of gastric acidity, it must be stressed, could be relied on to indicate the behavior of the effective acidity (expressed in terms of pH) in the duodenal bulb over the same period of time.

The average values given in Table I demonstrate that the oral administration of antacids in the commonly employed therapeutic dosages enhances the neutralizing ability of the contents of the first part

of the duodenum. The decrease in intraduodenal acidity, it will be noted, is not startling. The average values fail to indicate that the diminution of acidity in the duodenal bulb was of comparatively short duration and, in spite of its seeming superior action was followed in the instance of Sippy powder by a rebound increase in duodenal hydrogen ion concentration (Fig. 3) (3b). Furthermore, the in situ effects of antacids on duodenal acidity in patients with duodenal ulcer could not be accurately predicted from their behavior in the stomach.

In all the subjects studied, neutralization in the duodenal bulb under fasting conditions was as good (Table I) and in several ways was even better (Tables II, III, IV) than during the active digestion of various foodstuffs.

The fact that the gastric acidity was higher in fasting dogs than in fasting normal people (Table I) is surprising but not necessarily significant. It is possible that the stimuli affecting gastric secretion which were

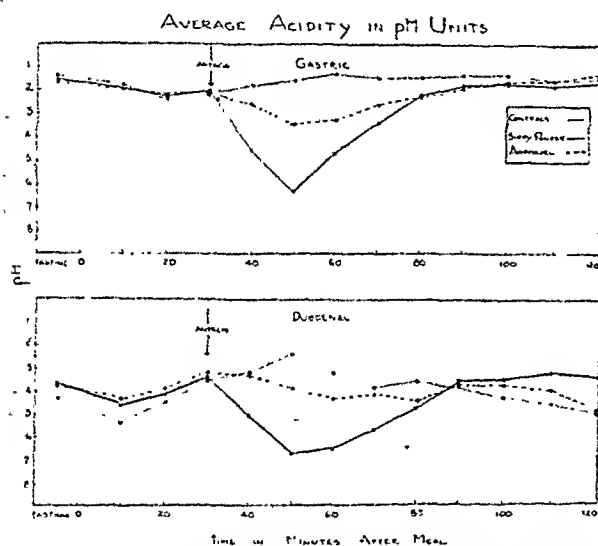


Fig. 3. Average acidity in pH units of samples collected simultaneously from just above and just below the pylorus in duodenal ulcer patients before and after the administration of antacids.

unavoidably associated with the experimental procedures may have been more effective in the dogs. Moreover, much greater variation in the degrees of gastric acidity are seen in normal human subjects than in dogs and the group average in the humans reflects the influence of their low acid values.

The opinion occasionally expressed in textbooks of physiology that the duodenal contents of the human are less acid than those of dogs receives no support from these results. In spite of the greater average gastric acidity in dogs there was no important difference in the acidity of the contents of the first part of the duodenum between dogs and normal people (Table I). Excess neutralizing ability was greater in the dogs. The fact that neutralization of gastric acid in the duodenal bulb is apparently more efficient in dogs than in man may be related to the fact that dogs rarely, if ever, display a spontaneous duodenal ulcer.

The question of the occurrence in the intestine of acidities adequate to serve as a stimulus for the regu-

lation of gastro-intestinal functions such as gastric tone and peristalsis, pyloric tonus, and pancreatic secretion is partially answered by these observations. Available evidence indicates that a pH of 3.0 or below in the duodenum is needed to affect gastric functions significantly (9, 10) and a pH of 4.0 or below to cause more than minimal stimulation of the pancreas (11). Although acidities below pH 3.0 in the duodenal

TABLE III

Percentage of duodenal samples with a pH of 3.0 or below

|                         | Fasting | Ewald Meal | Liebig's Extract—Histamine Meal | Cream Meal |
|-------------------------|---------|------------|---------------------------------|------------|
| Dogs                    | 14      | 9          | 19                              | 0.8        |
| Normal Human Subjects   | 21      | 24         | —                               | —          |
| Duodenal Ulcer Patients | 49      | 50         | —                               | —          |

samples were observed in these experiments (Table III), with the exception of ulcer patients they did not occur with a striking frequency, they were not present with sufficient regularity, nor were they of sufficient duration to account alone for the regulation of gastric emptying. On the other hand, acidities adequate to stimulate the pancreas (pH 4.0 or below) were more frequent in all the subjects studied (Table IV).

### CONCLUSIONS

The following conclusions are based on the knowledge gained from a study of all the data obtained which comprised 19,986 separate determinations. Of these data only representative samples have been presented.

1. The contents of the first part of the duodenum are endowed with a considerable capacity to neutralize,

TABLE IV

Percentage of duodenal samples with a pH of 4.0 below

|                         | Fasting | Ewald Meal | Liebig's Extract—Histamine Meal | Cream Meal |
|-------------------------|---------|------------|---------------------------------|------------|
| Dogs                    | 22      | 32         | 40                              | 2          |
| Normal Human Subjects   | 30      | 38         | —                               | —          |
| Duodenal Ulcer Patients | 61      | 61         | —                               | —          |

buffer and dilute the gastric chyme which commonly exceeds the physiological needs. Nevertheless, even in normal subjects, the duodenal bulb is an acid area and free acid is not an abnormal finding.

2. In patients with duodenal ulcer the neutralizing ability in the duodenal bulb is impaired but not wholly lost. Duodenal ulcer patients appear to differ from normal persons in the direction of a defectiveness in

the neutralizing capacity in the duodenal bulb as well as in the direction of gastric hyperacidity.

3. The acidity of the contents of the duodenal bulb is largely determined by the type of food undergoing digestion and is related only in part to the degree of the gastric acidity.

4. The acidity in the stomach and duodenal bulb are not sharply parallel. None of the customary measures of gastric acidity reliably indicate the behavior of the effective acidity (pH) present over the same period of time in the duodenal bulb.

5. The oral administration of antacids in the usual therapeutic dose to patients with duodenal ulcer reduces the acidity of the contents of the first part of the duodenum, but the reduction is neither great nor

long-lasting and may be followed by a rebound increase.

6. Duodenal bulb neutralization under fasting conditions equals, and in some respects surpasses, that observed during digestion.

7. The neutralizing power of the contents of the duodenal bulb in normal man is exceeded by that in normal dogs.

8. The acidity of the contents of the first part of the duodenum is generally insufficient to affect gastric motility significantly except in duodenal ulcer patients. In dogs and in normal human subjects as well as in duodenal ulcer patients it may be a factor in stimulating pancreatic secretion.

## REFERENCES

1. Berk, J. E., Rehfuess, M. E. and Thomas, J. E.: A Method for the Simultaneous Aspiration of the Contents of the Stomach and First Part of the Duodenum. *J. A. M. A.*, 119:259, 1942.
2. Berk, J. E., Thomas, J. E. and Rehfuess, M. E.: (a) The Reaction and Neutralizing Ability of the Contents of the Pyloric Antrum and First Part of the Duodenum in Normal Dogs Following an Ewald Meal. *Am. J. Physiol.*, 136:157, 1942. (b) The Effect of a Cream Meal on the Acidity and Neutralizing Ability of the Contents of the Duodenal Bulb in Normal Dogs. *Am. J. Physiol.*, 136:285, 1942. (c) Limitations in the Use of Color Indicators in Gastric Analysis. *Am. J. Dig. Dis.*, 9:106, 1942.
3. Berk, J. E., Rehfuess, M. E. and Thomas, J. E.: (a) The Effect of Ulcer on the Acidity and Neutralizing Ability in the Duodenal Bulb. *Arch. Int. Med.* (In press). (b) The In Situ Effects of Antacids in Duodenal Ulcer. *Arch. Int. Med.* (In press).
4. Berk, J. E., Thomas, J. E. and Rehfuess, M. E.: The Effect of Gastric Hypersecretion on the Reaction and Neutralizing Ability of the Contents of the First Part of the Duodenum in Normal Dogs. *Am. J. Dig. Dis.* (In press).
5. Eyerley, J. B.: Comparative pH Values Within the Stomach, Pylorus and Duodenum in Antacid Therapy. *Am. J. Dig. Dis.*, 7:451, 1940.
6. Lattimore, J. D., Gold, A. and Ebendorf, H. C.: The Wilhelmj Test Meal. *Am. J. Clin. Path.*, Tech. Supp., 4:24, 1940.
7. Morton, C. B.: (a) Observations on Peptic Ulcer. VI. Preliminary Report of Clinical Experiments with Gastro-Duodenal Analyses. *Am. J. Med. Sci.*, 177:65, 1929. (b) Observations on Peptic Ulcer. *South. Surg.*, 3:316, 1934.
8. Thomas, J. E.: An Improved Cannula for Gastric and Intestinal Fistulas. *Proc. Soc. Exper. Biol. and Med.*, 46:260, 1941.
9. Thomas, J. E. and Crider, J. O.: The Regulation of Gastric Emptying. *Va. Med. Month.*, 64:181, 1937.
10. Thomas, J. E. and Crider, J. O.: Inhibition of Gastric Motility Associated with the Presence of Products of Protein Hydrolysis in the Upper Small Intestine. *Am. J. Physiol.*, 126:28, 1939. Small Intestine. *Am. J. Physiol.*, 126:28, 1939.
11. Thomas, J. E. and Crider, J. O.: A Quantitative Study of Acid in the Intestine as a Stimulus for the Pancreas. *Am. J. Physiol.*, 131:349, 1940.
12. Thomas, J. E., Crider, J. O. and McGinn, C. J.: A Study of Reflexes Involving the Pyloric Sphincter and Antrum and Their Role in Gastric Evacuation. *Am. J. Physiol.*, 108:683, 1934.
13. Wilhelmj, C. H., O'Brien, F. T. and Hill, F. C.: An Improved Gastric Test Meal. *Am. J. Dig. Dis. and Nutr.*, 3:319, 1936.

# The Relationship Between Gastro-Duodenal Motility Phases and Symptoms Associated With Duodenal Ulcer in the Human\*

By

THOMAS L. PATTERSON, Ph.D.

and

DAVID J. SANDWEISS, M.D.

DETROIT, MICHIGAN

**I**N a previous report (1) in which an attempt was made to correlate synchronous gastric and duodenal motility phases with the normal hunger sensation in man, it was demonstrated that the normal human subject presents four different phases of gastro-duodenal motility (using the dual balloon-kymograph-bromform manometer method) namely:

(1) Simultaneous gastric and duodenal motility—in which both the stomach and duodenum are exhibiting motility synchronously;

(2) Duodenal motility with a quiescent stomach—in which the duodenum exhibits motility at a time when the stomach is quiescent;

(3) Simultaneous gastric and duodenal quiescence—in which both the stomach and duodenum are in complete rest at the same time, and

(4) Gastric motility with a quiescent duodenum—in which the stomach exhibits motility at a time when the duodenum is at rest.

The recordings indicated conclusively that hunger sensations occur only during the first two of the above four gastro-duodenal phases, namely when both the stomach and duodenum are exhibiting motility, and when the duodenum alone is exhibiting motility. In this communication similar studies are presented on patients with active duodenal ulcer, in an effort to correlate ulcer distress in relation with these four phases of gastro-duodenal motility.

## LITERATURE

References to literature in the field of gastro-intestinal physiology, in so far as the authors have been able to determine, indicate that this is the first study to be made on the synchronously recorded gastro-duodenal motility phases in ulcer patients.

Eighty years ago, Busch (2) made observations on an extremely emaciated woman with a duodenal fistula. Because this woman was so emaciated he was able to observe the movements of the stomach and intestines in detail through the abdominal wall. In this subject, Busch observed in the empty intestines, periods of

\*Read at the Annual Meeting of the American Gastro-Enterological Association at Atlantic City, N. J., June 8-9, 1942.

From the Department of Medicine, Harper Hospital, Detroit, and Department of Physiology, Wayne University, College of Medicine, Detroit.



DUAL APPARATUS FOR RECORDING MOTILITY OF STOMACH AND DUODENUM

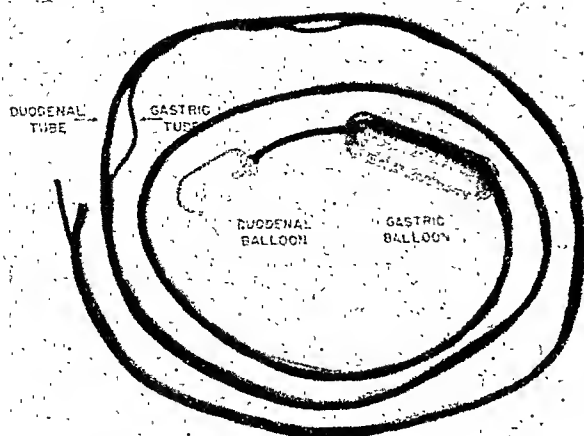


Fig. 1. Dual apparatus for recording synchronous gastro-duodenal motility.

active intestinal peristalsis alternating with periods of rest without any regularity in the recurrence of these active periods. In later years, Boldyreff (3), Carlson (4), and Ivy and Vloedman (5), have reported similar observations on intestinal motility.

Ginsberg, Tumpowsky and Hamburger (6) have given experimental evidence that muscle tension represents an adequate factor in the production of ulcer pain. Carlson (7) in a publication a few months later definitely correlated graphically ulcer pain with hunger contractions by means of a balloon in the stomach and a signalling device operated by the subject. He showed that intermittent ulcer pain was synchronous with gastric contractions, and Carlson concluded that the pain was due, not to the acidity *per se*, but to muscle tension. Hardt (8) on the basis of similar work arrived at the same conclusion. Poulton (9) found that the distress of gastric ulcer could be initiated by increasing gastric tension, and relieved by its reduction. Hurst's (10) findings ascribed the pain to muscle tension. Ryle (11) is of the opinion that "given an irritative focus," food ingestion, or readiness to receive it, even in the absence of acid secretion, forms an adequate stimulus for the initiation of an exaggerated tonic and peristaltic action upon which the pain depends.

Homans (12) took issue with the muscle tension view and contended that powerful, vigorous contractions of the fundic portion of the stomach may be present without pain and pain without fundic contractions. Ortmayer (13) concluded from her findings that ulcer pain is not related to muscle tension, but to the acidity of the gastric content.

The majority of workers have found that hunger contractions of ulcer patients are normal, or only slightly exaggerated (14), but Onodera, Kanegae, Matufuzi and Hasi (15) have described a type of augmented motility which they believe is typical of this disorder. The development of ulcer pains from normal hunger contractions is usually ascribed to concomitant hyperexcitability of the sensory mechanism in the gastro-intestinal wall, which may result from gastritis, swelling and inflammation surrounding the

ulcer, acid irritation, or other similar factors (16, 17). Furthermore, Reynolds and McClure (18) on the basis of their roentgenologic studies, concluded that there was no evidence of the relationship of ulcer pain to motor activity.

The hypersensitivity of the gastro-intestinal wall, is, in general accord with the significant observations of Dragstedt and Palmer (19) of a patient with a duodenal ulcer exposed under local anesthesia. Gentle rubbing of the serosa over the ulcer scar with the finger produced pain similar to ulcer distress which persisted after the rubbing had ceased. Compression or massage of the ulcer area, as well as traction on the duodenum also produced severe distress, but was relieved on the introduction of sodium bicarbonate into the stomach, even though the traction was continued. The introduction of 0.5% hydrochloric acid into the first part of the duodenum caused the ulcer distress to return, but this was again relieved by sodium carbonate. Somewhat later, a deep circular contraction ring developed just distal to the ulcer and this was succeeded by several similar spasms of the duodenum, which were accompanied during the spastic periods by severe, cramp-like pain. Palmer (20) has also reproduced "ulcer pains" in some of his patients by inflation of the balloon at various levels of the intestine.

Wheelon and Thomas (21) employing an enterograph introduced into the pyloric canal and antrum through an incision in the fundic portion of the stomach made direct graphic and radiographic observations on dogs. Their results showed that the antrum and pyloric sphincter were rhythmical in action, that



Fig. 2. The arrows point to the ends of the two tubes. The one at the right is in the stomach; the one to the left in the second portion of the duodenum. The inflated balloon in the stomach is not distinct because of the density of the vertebrae.

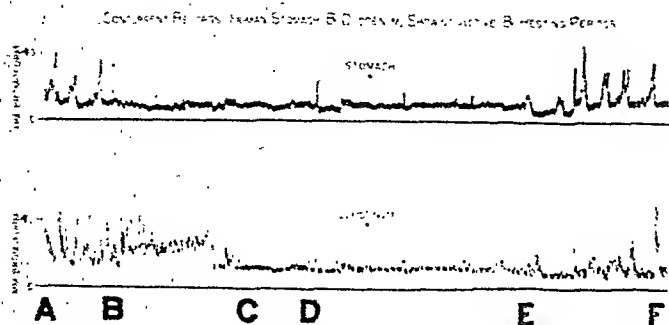


Fig. 3. (1) A-B: Synchronous gastric and duodenal activity. (2) B-C: Duodenal activity with a quiescent stomach. (3) C-D: Quiescent duodenum and quiescent stomach. (4) D-F: See text. [For 4th phase (quiescent duodenum and active stomach) see Fig. 4, B-C].

is, contractions and relaxations followed each other in a regular sequence. Therefore, the phase of activity in the sphincter are such as to supplement those of the antrum. These same authors (22) in a later publication, using a compound enterograph studied the relation of duodenal activity to that of the pars pylorica in dogs. They found that the pyloric antrum and sphincter showed cycles of rhythmical motility and to these the duodenal rhythm was closely related, thereby functionally supplementing the activities of the antrum.

Ivy and Vloedman (5) made simultaneous graphic recordings of gastric and duodenal motility on normal men and dogs, using a single balloon in the duodenum and another in the stomach. Their results showed that the duodenum during hunger manifested contractions synchronous with those that occurred in the stomach with the exception that frequently the duodenal contractions lagged behind those of the stomach. The authors are of the opinion, that the duodenal contraction is due only to the passage of the gastric hunger contractions, or their effect, from the stomach to the duodenum. Quigley and Solomon (23) studied graphically the effect of the action of insulin on the motility of certain portions of the gastro-intestinal tract (stomach and duodenum) on a normal man and dogs. The activity of the intestine was recorded with either a single or a dual balloon in the duodenum and this activity was correlated with the response of the stomach by making simultaneous records from a single or a triple balloon (24) introduced into the stomach. The evidence obtained from this investigation again proves that duodenal motility occurs synchronously with gastric motility, but in addition, it has been

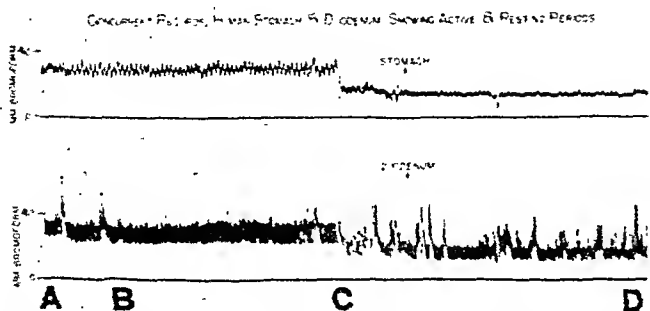


Fig. 4. (1) A-B: Synchronous gastric and duodenal activity. (2) B-C: Quiescent duodenum with active stomach. (3) C-D: Duodenal activity with a quiescent stomach. Note: Fig. 3, A-B; B-C and C-D, also Fig. 4, B-C represent four gastro-duodenal motility phases.

further shown that duodenal hunger contractions can occur in the absence of gastric motility.

### METHOD OF STUDY

The studies in this investigation were conducted on four human male patients, one white and three colored, whose ages and duration of duodenal ulcers were as follows, namely—F. S., 21, ulcer since 1939; O. R., 37, ulcer since 1935; H. B., 55, ulcer since 1937, and T. A. J., 68, ulcer since 1934. These individuals were fasted from 18 to 20 hours to assure an empty stomach but were permitted to take water, so the factor of thirst did not enter.

The motility of the fundic region of the stomach and of the second segment of the duodenum were



Fig. 5. X-ray picture of duodenal ulcer. Mr. O. R., age 37—ulcer history of 2½ years' duration. Roentgenogram shows a marked deformity of the duodenal cap, with pseudodiverticuli of the anterior wall, and star-shaped rugae typical of duodenal ulcer.

recorded synchronously by means of a dual balloon system. This system consists of two rubber balloons attached to two rubber tubes. The lower end of the smaller gastric tube containing a short metal cuff shown in the roentgenogram of Fig. 2 was cemented into the upper end of the gastric balloon. The longer duodenal tube also enters the upper end of the gastric balloon in close proximity with the smaller tube where it is cemented and made secure to the first tube with silk windings. It then passes through the lumen of this balloon and beyond without making air connection therewith, the lower end of the stomach balloon being tied to this tube five inches below the point of its first attachments. A metal tip was inserted into the end of the larger tube to which was attached a smaller duodenal balloon (see Fig. 1). By means of this recording

system, the activity of both the stomach and the duodenum could be obtained synchronously.

After trying out balloons of varying capacities, it was concluded that a gastric balloon about five inches in length and a duodenal balloon two and one-half to three inches in length prepared from a condom of very thin rubber was the most suitable for our type of experimentation. However, we did employ in some experiments, both on the normal subjects and the

During the early phases of our experimentation we experienced difficulty and considerable delay in the passage of the duodenal balloon out of the stomach and into the duodenum, until one day through a co-incidence we were given a cue. It was in the early fall, and the patient after swallowing the balloons was lying on the cot. The window was open and the air entering the room was cool. The patient, though protected from the window by a tall screen at the head of the cot, suddenly remarked that the room seemed cool. The window was thus closed. In a few minutes the patient complained of having a cramp in one leg, and attributed it to the coolness of the room. The room soon became comfortable for the patient but the duodenal balloon remained in the stomach the rest of the day as determined by several fluoroscopic examinations. We, therefore argued, that if a lowered temperature was defeating our purpose, (probably through a constriction of the pyloric musculature), heat should produce the opposite effect in relaxing the

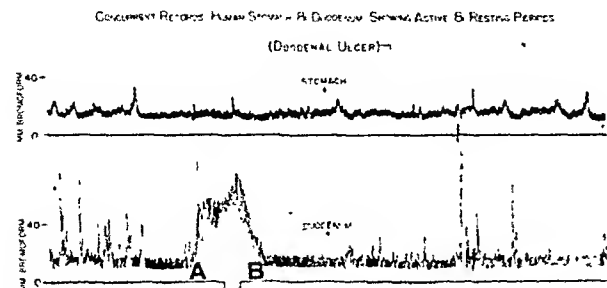


Fig. 6. A-B: Ending of a period of duodenal activity in strong incomplete tetanus (with a quiescent stomach). The patient experienced ulcer distress during this phase as indicated by the signal. The duodenal activity frequently terminated in incomplete tetanus. The gastric activity in the young adults usually also ends in incomplete tetanus.

ulcer patients a duodenal balloon four centimeters in length which graphically gave us practically identical results. Experience indicated that a distance of three inches between the two balloons more suitably met the conditions of our experimentation. The entanglement and kinking of the rubber tubes were prevented by cementing thin-one-quarter inch bands cut from condom rubber around the tubes at distances of every four inches. Both the gastric and duodenal tubes are opaque to X-ray. Their location can thus be determined easily by fluoroscopy.

In our experiments the dual balloons above described were introduced by the esophageal route into the stomach. The patients were then requested to lie down on a cot on their right side and remain in that position for about an hour, when they were given a fluoroscopic examination to locate the positions of the respective balloons in the gastro-intestinal tract. If the examination showed the duodenal balloon to be located in the second segment of the duodenum it was inflated and the end of the tube tightly clamped off. The gastric balloon was checked and inflated in a like manner (see Fig. 2). However, if the duodenal balloon had been carried too far into the duodenum, or if the gastric balloon had been carried into the duodenum, (as it sometimes occurred), the position of the balloons were adjusted by pulling on the tubes and then inflated in their proper positions. If the duodenal balloon had not been carried into the duodenum, the patient was required to repeat the former procedure on the cot for another hour. In fact, no graphic registrations of gastro-duodenal motility phases were included in this study unless the exact location of the balloons had been determined fluoroscopically at the beginning of the experimental period. The recording periods ranged from two hours to nine and three-quarter hours.

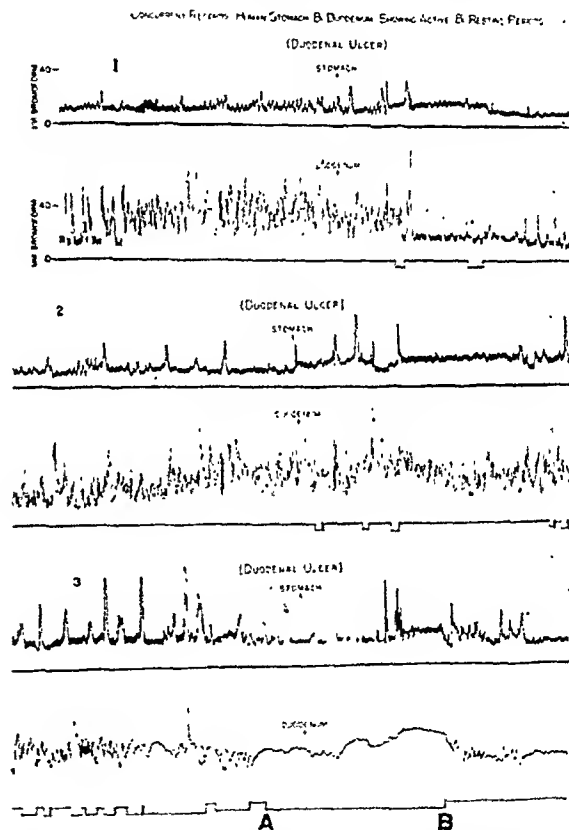


Fig. 7. Tracings 1, 2 and 3 represent continuous synchronous gastro-duodenal motility phases during 2 1/2 hour study. Note signalling of ulcer distress, recorded by the patient at the bottom of the tracing. These increase in frequency and duration and occur only when the duodenum is in an active phase, the stomach being either active or quiescent. Note signalling of ulcer pain represented by A-B of tracing 3, which lasted for about 18 minutes. The patient was extremely uncomfortable, complaining bitterly of epigastric pain explained by him as typical of ulcer. The duodenum during that period exhibited a marked increase in tonus and passed into a state of incomplete tetanus which continued until the pain ceased. With the cessation of pain the duodenum relaxed and continued its activity.

CONCURRENT RECORDS, HUMAN STOMACH—SHOWING ACTIVE & RESTING PERIODS

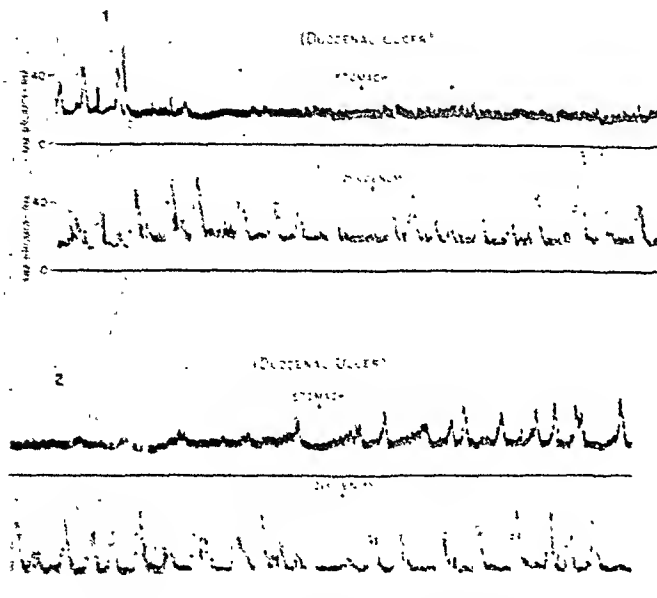


Fig. 8. Tracings 1 and 2 represent continuous, synchronous gastro-duodenal motility phases over a period of 1½ hours, showing that the duodenum may at times continue its activity through an entire period of gastric quiescence. The duodenum was active in the preceding active gastric period (not shown on this recording) as well as in the active period following the period of gastric quiescence.

same musculature. Therefore, in our next experiment immediately after swallowing the tubes, we wrapped two hot blankets around the patient, before taking the position on the cot described above. In addition, we urged the patients to drink warm water not only during the procedure of swallowing the balloons, but also during the interim while we were waiting for the duodenal balloon to pass out of the stomach into the duodenum. Since adopting these measures, we have had comparatively little difficulty as against our original experiences.

As soon as the patient's fluoroscopic examination was found satisfactory, connecting tubes from the respective balloons were attached to separate bromoform (sp.g 2.884) manometers for recording synchronously the gastro-duodenal motility phases. A long paper kymograph was used carrying sufficient paper for continuous recordings for periods of five to eight hours without changing. The kymograph speed employed in this experimentation was at the rate of 60 minutes per revolution per single drum of a Harvard kymograph. The ink method of recording (25) developed by one of us (T. L. P.) was employed in this series of experiments. Two signal magnets were employed: One was to trace a base line under the gastric motility curve, and the second (lower) signal was used for the same purpose under the duodenal motility curve. In addition, an electric signalling device, operated by the patient to record his ulcer distress periods, was employed the recording apparatus of which was screened off from the patient.

In some of the earlier experiments in which gastric motility alone was recorded, it was desired to introduce certain substances such as the Sippy Powder No. 2 directly into the stomach, without the knowledge of the patient. A second tube was therefore, attached to the gastric balloon tube. Under such circumstances

it was possible to introduce liquids directly into the stomach to determine their effect on the tonus and gastric motility as well as the effect on ulcer distress.

It will be observed that the tracings (illustrations) have both time and pressure scales. This enables one to estimate time factors and bromoform manometric pressures. The number of millimeters on the bromoform scale X2 will give either the graphic recording pressure, or the amplitude (strength) of contraction.

## RESULTS

(1) The four phases of synchronous gastro-duodenal motility listed above for the normal human subject are also exhibited by patients with duodenal ulcer (see Fig. 3, A-B; B-C and C-D, also Fig. 4: B-C for the normal subject).

(2) Previously it was shown (1) that in the normal human subject, duodenal activity differs somewhat from gastric activity when both are synchronously recorded (see Fig. 3, D-F). These variations (between gastric and duodenal activity) also occur in patients with duodenal ulcer. They are: (a) The period of duodenal activity usually ends (as does the period of the young adults' stomach) in strong incomplete tetanus. However, the duodenum continues its activity usually from 10-12 minutes after the stomach has completed its active period (see Fig. 3, B-C). (b) the duodenum after a short period of quiescence, lasting between 8 and 18 minutes, (Fig. 3, C-D.), begins an active period with small contractions, while the stomach is still in the quiescent state (see Fig. 3, D-E). The small duodenal contractions gradually increase in amplitude and develop greater activity

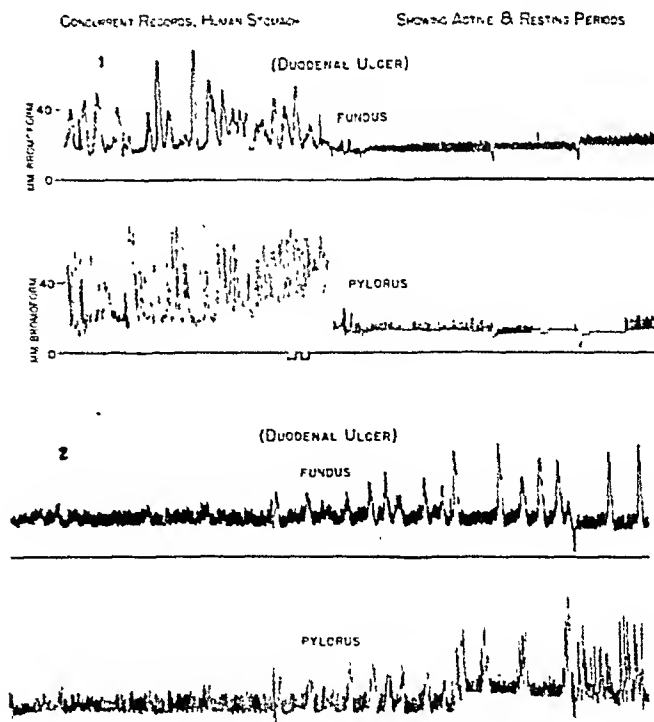


Fig. 9. During the study on this patient, the distal balloon did not reach the duodenum although the usual measures were employed. Fluoroscopic examination in this case was not made at the beginning but was made at the end of the study when fluoroscopy showed that one balloon was in the fundus and the other in the antrum. Note: That the activity in both regions of the stomach begins and ends synchronously.

when the stomach becomes active (see Fig. 3, E-F). (c) In some cases, the duodenal motility may continue through the entire gastric quiescent period and also continue through the next gastric activity period before it terminates (see Fig. 8). (d) At times, the stomach tends to exert an augmentative influence on the duodenal motility as shown by the increase in the amplitude of the individual duodenal contractions (Fig. 3, E-F). During gastric quiescence the reverse was noted at times (Fig. 3, D-E). (e) Duodenal activity may begin when the stomach is still in a quiescent phase (see Fig. 3, D-E). This would suggest that duodenal activity is not dependent on gastric motility but rather, that it has an "autonomous" activity.

(3) It will be noted from the tracings that patients experienced ulcer distress either when the stomach and duodenum were both exhibiting motility or when the duodenum alone exhibited motility (see Figs. 6 and 7). At no time during the studies did the patient indicate by the electric signaling device ulcer distress when the duodenum was quiescent (see Fig. 6, A-B and Fig. 7). It is interesting to note that hunger contractions similarly occurred during these two phases of activity. The duration of ulcer distress however was considerably longer.

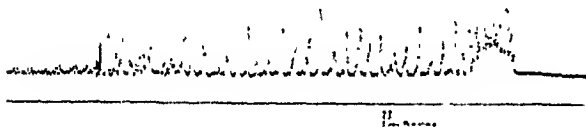


Fig. 10. At the point of arrows, the original Sippy powder No. 2 dissolved in 2 ounces of water was administered through a tube without knowledge of the patient. Note, that this solution had no effect on the tonus and amplitude of gastric contractions. Similar studies are now being conducted to determine its effect on duodenal activity.

In the early phases of the work, it was expected that ulcer distress would also occur during a quiescent duodenum but active stomach. This, however, was not observed. Failure to obtain such recordings by the method employed in 21 studies, conducted on four different (duodenal) ulcer patients (in all 75 hours\* of actual synchronous motility recordings) would suggest that duodenal activity may be one of the factors in ulcer distress.

(4) Fig. 7, parts 2 and 3 shows gastric and duodenal activity during severe (duodenal) ulcer distress. It will be noted that when ulcer distress is of severe degree, lasting anywhere from a few minutes to 2 hours or longer (patient moaning in pain, etc.), both the gastric and duodenal curves become so irregular that the actual beginning or ending of these active motility periods can not be determined (see Fig. 7, parts 2 and 3 A-B). This does not occur in mild ulcer distress.

(5) During several studies, alkalies (Sippy powder No. 2) were introduced directly into the stomach through a separate tube without knowledge of the patient. While alkalies relieve ulcer distress, no inhibitory effect was noted either on the gastric tonus or gastric motility (see Fig. 10). Further studies

with alkalies will be conducted to determine whether these have any effect on duodenal activity.

## DISCUSSION

The motility studies on the human stomach and the duodenum (second segment) recorded synchronously by the dual balloon bromoform manometer method have shown conclusively the existence of four distinct gastro-duodenal phases, and that these are present in both the normal individual, as well as in patients with duodenal ulcer (see Figs. 3, 4, 6, 7 and 8 with descriptive captions). Furthermore, when these motility phases are studied in relation to the occurrence of ulcer distress, the results of this investigation have shown unequivocally that ulcer distress occurs only when both the stomach and duodenum are simultaneously exhibiting motility, or when the duodenum alone is exhibiting motility. Ulcer distress did not occur in the third and fourth gastro-duodenal phases, i. e., when the duodenum is in a quiescent phase. *In other words, these studies so far indicate that the duodenum must be in an active motility phase for the duodenal ulcer patient to experience ulcer distress.*

While the tracings definitely indicate that duodenal activity must be present for the patient to experience ulcer distress and that abnormal duodenal motility phases occur when the patient experiences severe ulcer pain they should not necessarily be interpreted as indicating that duodenal motility is the only factor responsible for ulcer distress. They merely focus our attention on the fact that definite abnormal physiological phenomena are taking place in the duodenum, (when a duodenal ulcer is present), and that the duodenum, rather than the stomach, should receive our attentions. However, a disturbed duodenal motility is probably only one of the factors in ulcer distress. Other factors, in relation to the duodenum, that must be considered and studied are: the acid or alkaline concentration of the duodenal juice, the presence or absence of duodenal regurgitation, the normality or abnormality of the pancreatic enzymes and bile that enter the duodenum, the potency of duodenal hormones such as enterogastrone, etc., etc.

The motility of the duodenum sometimes develops its period of activity long before the stomach resumes its active period. This would indicate that the duodenum acts independently of the stomach. If we can assume that this is the case, it would be in accordance with the view, that the small intestine possesses a high degree of autonomy, or independence of function, which is probably to a large degree dependent on the myenteric nerve plexus. If the duodenum through its automatism plays such a role physiologically, it might easily initiate and control the ending of its active motility phase, as well as being a contributing factor in initiating and controlling duodenal contractions while the stomach is in a state of complete rest.

## SUMMARY

(1) Twenty-one synchronous gastro-duodenal motility studies are presented on four patients with duodenal ulcer, in all approximately 75 hours of actual synchronous motility recordings. The dual balloon kymograph bromoform manometer method was employed. The patients recorded ulcer distress on the kymograph by means of an electric signalling device.

(2) The four phases of synchronous gastro-duo-

\*Our experiences with motility studies (gastric and duodenal) in relation to ulcer distress actually consists of 75 hours of actual recordings on 4 ulcer patients and one normal subject (in all approximately 75 hours of actual recordings).



denal motility previously found to exist in the normal subject was also found to exist in the patients with duodenal ulcer.

(3) Ulcer distress, experienced by the patients during the course of these studies, was recorded by them only during periods when the duodenum was in an active state of motility regardless of the state of the gastric phase. The stomach was either in quiescence or in activity when ulcer distress was recorded.

(4) When the ulcer patients experienced severe epigastric (ulcer) pains of relatively long duration (15-18 minutes or longer) there was a definite abnormality in the duodenal activity. The duodenum passed into a state of increased tonus simulating a condition of incomplete tetanus.

(5) While it was found that gastric motility may at times augment duodenal activity, it was also found that the duodenum at times initiates a period of activity when the stomach is in a quiescent state. This would appear to indicate that the duodenum possesses autonomy of action, and its period of activity and quiescence may be entirely independent of the stomach.

(6) It is not the intention of the authors to convey the impression that abnormal duodenal motility is the only factor involved in duodenal ulcer distress. Other factors in relation to the duodenum, the site of the ulcer, must be taken into consideration, and these should be studied in relation to ulcer distress and duodenal activity. The other factors to be studied are: the acid or alkaline concentration of the duodenal juice, the presence or absence of duodenal regurgitation, the normality or abnormality of the pancreatic enzymes and bile that enter the duodenum, the potency of duodenal hormones, such as enterogastrone, etc., etc.

In other words, it appears to us, that abnormal physiologic phenomena are taking place in the duodenum, when a duodenal ulcer is present, and these should receive more of our attention than heretofore.

Note: We wish to express our appreciation to the Roentgenologists of the X-ray Department at Harper Hospital, Detroit, for their valuable assistance during the course of this work.

## REFERENCES

1. Patterson, T. L. and Sandweiss, D. J.: The Simultaneous Gastric and Duodenal Motility Phases in Man. *Federation Proceedings*, Vol. 1, Part II, No. 1, pp. 66, March 16, 1942.
2. Busch, W.: Beitrag zur Physiologie der Verdauungsorgane. *Arch. f. Pathol. Anat.*, Vol. 14, p. 140, 1862.
3. Beldyreff, W.: Le Travail periodique de l'appareil digestif en dehors de la digestion. *Arch. d. Sci. Biol.*, Vol. 11, pp. 1-5, 1905.
4. Carlson, A. J.: The Control of Hunger in Health and Disease. The University of Chicago Press, Chicago, pp. 1-319, 1916.
5. Ivy, A. C. and Vloedman, D. A.: The Small Intestine in Hunger. *Am. J. Physiol.*, Vol. 72, No. 1, pp. 99-108, March, 1925.
6. Ginsburg, H., Tumpowsky, I. and Hamburger, W. W.: Contributions to the Physiology of the Stomach. XXXV. The Newer Interpretation of the Gastric Pain in Chronic Ulcer. *J. Am. Med. Ass'n*, Vol. 67, pp. 990-994, Sept., 1916.
7. Carlson, A. J.: Contributions to the Physiology of the Stomach. XLIV. The Origin of the Epigastric Pains in Cases of Gastric and Duodenal Ulcer. *Am. J. Physiol.*, Vol. 45, No. 1, pp. 81-91, Dec., 1917.
8. Hardt, L. L. J.: Pain in Active Pathologic Processes in Stomach or Duodenum. *J. Am. Med. Ass'n*, Vol. 70, p. 837, March, 1918.
9. Poulton, E. P.: An Investigation of the Cause and Relief of Pain in Gastric Ulcer. *Lancet*, Vol. 1, p. 263, Feb., 1921.
10. Hurst, A. F.: The Sphincters of the Alimentary Canal. *Brit. Med. J.*, Vol. 1, p. 145, Jan., 1925.
11. Ryle, J. A.: Gastric Function in Health and Disease. Oxford University Press, London, pp. 1-147, 1926.
12. Homans, J.: The Relation of Pain in Gastric and Duodenal Ulcer to Muscular Activity of the Stomach. *Am. J. Med. Sci.*, Vol. 157, p. 74, Jan., 1919.
13. Ortmeier, M.: Gastric Motor Activity in Patients with Peptic Ulcer. *Arch. Int. Med.*, Vol. 35, p. 423, April, 1925.
14. Quigley, J. P.: Motor Physiology of the Stomach, the Pylorus and the Duodenum with Special Reference to Gastro-Duodenal Ulcer. *Arch. Surg.*, Vol. 44, pp. 414-437, March, 1942.
15. Onodera, N., Kanecae, S., Matufuzi, M. and Hasi, T.: Ueber die gastroskopische Methode der Diagnose von Magenkrebs, Mangel-Darm-Geschwür und Cholecystitis. *Ztschr. f. klin. Med.*, Vol. 118, p. 354, 1931.
16. Palmer, W. L.: The Mechanism of Pain in Gastric and Duodenal Ulcers. I. Achlorhydria. *Arch. Int. Med.*, Vol. 38, No. 5, pp. 603-611, Nov., 1926.
17. Palmer, W. L.: The Mechanism of Pain in Gastric and in Duodenal Ulcer. II. The Production of Pain by Means of Chemical Irritants. *Arch. Int. Med.*, Vol. 38, No. 6, pp. 694-707, Dec., 1926.
18. Reynolds, L. and McClure, C. W.: Motor Phenomena Occurring in Normal Stomachs, in Presence of Peptic Ulcer and Its Pain, as Observed Fluoroscopically. *Arch. Int. Med.*, Vol. 29, pp. 1-11, Jan., 1922.
19. Dragstedt, L. R. and Palmer, W. L.: Direct Observations on the Mechanism of Pain in Duodenal Ulcer. *Proc. Soc. Exper. Biol. and Med.*, Vol. 29, No. 6, pp. 753-755, March, 1932.
20. Palmer, W. L.: The Mechanism of Pain in Gastric and in Duodenal Ulcer. III. The Role of Peristalsis and Spasm. *Arch. Int. Med.*, Vol. 39, No. 1, pp. 109-133, Jan., 1927.
21. Wheelon, H. and Thomas, J. E.: Observations on the Motility of the Antrum and the Relation of Rhythmic Activity of the Pyloric Sphincter to That of the Antrum. *J. Lab. and Clin. Med.*, Vol. 6, No. 1, pp. 124-143, Oct., 1920.
22. Wheelon, H. and Thomas, J. E.: Observations on the Motility of the Duodenum and the Relation of Duodenal Activity to That of the Pyloric Sphincter. *Am. J. Physiol.*, Vol. 59, No. 1, pp. 72-96, Feb., 1922.
23. Quigley, J. P. and Solomon, E. I.: Action of Insulin on the Motility of the Gastro-Intestinal Tract. V. a. Action of the Human Duodenum, b. Action on the Colon of Dogs. *Am. J. Physiol.*, Vol. 91, No. 2, pp. 488-495, Jan., 1930.
24. Quigley, J. P., Johnson, V. and Solomon, E. I.: Action of Insulin on the Motility of the Gastro-Intestinal Tract. I. Action on the Stomach of Normal Fasting Man. *Am. J. Physiol.*, Vol. 90, No. 1, pp. 89-98, Sept., 1929.
25. Patterson, T. L.: A Satisfactory and Economical Kymographic Ink-Recording Pen with an Electric Indicator Attachment. *Kongressbericht II des XVI. Internationalen Physiologen-Kongresses Zürich (Schweiz)* pp. 5-6, Aug., 1938.

## DISCUSSION

DR. J. EARL THOMAS (Philadelphia): I wish to discuss Dr. Berk's paper. If acid is the cause of duodenal ulcer, then one or more of three things must be true:

(1) There is some special susceptibility of the duodenum so that normal acidity will cause an ulcer, in which case the cause isn't acid at all; it is only an accessory factor; or

(2) There must be an excessive amount of acid secreted by the stomach; or

(3) There must be some failure of neutralization of gastric acid in the duodenum.

The investigations of gastric acidity in the presence of duodenal ulcer have not given a very satisfactory indication that hyperacidity in the stomach is sufficient to cause ulcer. Many normal people, as we all know, have a higher gastric acidity than many ulcer patients.

The important point, it seems to me, in Dr. Berk's study is the finding that in ulcer patients there is a higher duodenal acidity than in normal individuals, higher even than in those normals who have a gastric acidity as great or greater than the average of ulcer patients. This suggests that in these patients, there is some defect in the duodenal neutralization of gastric acid.

It is true that in the averages this defect didn't appear very great. Dr. Berk said it was probably not statistically significant, but in the individual curves there was evidence of wide fluctuations in the acidity of the duodenal contents which did not occur to the same extent in normal individuals; consequently there were periods of greater than normal acidity, and these periods lasted longer than they did in normal persons. It is possibly not necessary that the duodenal acidity should remain high for a long period of time to do injury if the increase over the normal is sufficiently great and occurs with sufficient frequency. I think the point of greatest clinical significance in this study is the finding of a defect in duodenal neutralization of gastric acid.

DR. WALTER L. PALMER (Chicago): Mr. President, unfortunately I was detained and didn't have the opportunity to hear the paper by Captain Berk and his associates, but there are some remarks I should like to make on so-called hyperacidity, remarks prompted by the discussion by Dr. Thomas. I think it has been pretty well shown



that the normal stomach secretes in response to test meals a fluid as acid as that found in peptic ulcer; therefore, we cannot look for the cause of peptic ulcer in so-called hypersecretion, secretion of the gastric juice more acid than the normal stomach secretes. This fact does not prove that acid has nothing to do with the cause of ulcer, for the reason Dr. Thomas brought out.

I was very much interested to hear that Captain Berk and his associates have found these more acid periods in the duodenum. It seems to me that this observation fits in very well with the thought that there may be a great abundance of acid gastric secretion, a greater quantitative secretion, particularly in terms of the total twenty-four hour period than occurs in the normal individual.

Such ideas are supported by many pieces of work done in the past, such as Dr. Winkelstein's. I had the pleasure of reading the paper sent over by Dr. Sandweiss just a few days ago, in which he had also shown this increased quantity of acid gastric secretion at night in patients with peptic ulcer.

With regard to pain the normal stomach can be the source of pain, of hunger pains, as we all know, but the pain of ulcer seems to be something different from the normal hunger pain. It is usually, when present, continuous for a number of minutes, fifteen or twenty minutes, for an hour or more, not as intermittent as most of the pains which Dr. Patterson showed. Something happens which lowers the pain threshold of the stomach in ulcer.

I think we can be pretty confident that the site of the pain is the region of the ulcer. There is pretty good evidence now, it seems to me, that inflammation is capable of lowering the pain threshold. Presumably in an ulcer, surrounded by inflammation of a chemical type, the pain threshold of the nerve endings is lowered.

In this lesion pain may be induced by either chemical or mechanical stimuli. The application of acid to the ulcer will evoke pain, when it is sufficiently sensitive. The contractions about the ulcer, peristalsis, or spasm, will evoke pain under such circumstances as Dr. Patterson has just shown you.

I think—it has been my experience, in fact—that if one maintains an alkaline or neutral medium for several hours, one can desensitize this pain threshold and one can then have powerful peristaltic waves such as Dr. Patterson found, which are painless, whereas previously they had been painful. In other words, the presence of acid seems to me to be essential for the formation of the ulcer, for the production of the inflammation which is essential for lowering of the pain threshold and it ordinarily, in my judgment and experience, is the stimulus which sets off the pain mechanism, but contraction or spasm likewise can set off this pain mechanism.

DR. MARTIN W. REHFUSS (Philadelphia): Mr. President, Ladies and Gentlemen: This question has been a very interesting one to us because several years ago Dr. Eads, Dr. Thomas and I reported the motility of the antrum and the cap of the duodenum.

It is very difficult, we found, to anchor balloons in the antrum and the cap of the duodenum; nevertheless, there is so much significant evidence regarding the question and the importance of gastric acidity—now we believe that four out of five duodenal ulcers have a relatively high gastric acidity of a certain type, and we also believe that that figure is preceptibly higher than it is in the normal individual; nevertheless, I have never been convinced, though I was impressed, by Martin's studies, in which he spoke of the acid threshold in the duodenum, which was shifted to the right or to the left.

Now, I said to Captain Berk, even before he started this work, that I thought the most important thing was to have the exact position of this intubation, and for that reason Captain Berk, who is a very careful worker, was

able to locate very carefully both the cap and the antrum, so he got from that area, and from that area a supplementary extraction from both portions.

Now, the amazing thing to see in these experiments is the fact that the acidity on this side is so rapidly changed on that side. It is an amazing thing to note, in other words, that there is not only normal or free acid in most normal cases, but there is also this very sudden change in the normal individual, which takes place from the antrum over on this side.

Now, the interesting thing to me is what causes that sudden change. Personally, I can't see any other explanation for that sudden change unless it be this pancreatic mechanism; in other words, what else could account for a drop as sudden as that over an area scarcely an inch in distance?

Now, unfortunately, none of these experiments emphasize the fact as to what happened to the pancreatic mechanism, and in work we are doing in the second portion of the duodenum, there are no accurate methods for estimating how much of that secretion is pancreatic secretion.

Dr. Berk did not mention the interesting thing regarding the effect of food on this area, and I personally think this big, forward advance we have to find out is to transfer our affections from the stomach and gastric acidity to the duodenum and the site of the ulcer, where we can find out precisely what is going on in that particular area.

DR. J. EDWARD BERK (Captain J. Edward Berk, Tilton General Hospital, Fort Dix, N. J.): Mr. President, we were impressed at the outset by the fact that the huge body of work which had been done concerning the acid factor in duodenal ulcer had been confined almost entirely to the acidity in the stomach. Much was assumed, yet nobody had any accurate knowledge regarding the actual course of events in the important ulcer-bearing duodenal bulb where most clinical ulcers occur. It was for the prime purpose of supplying some such knowledge that this study was undertaken.

Dr. Palmer mentioned, and I know he is correct, that duodenal ulcer patients in contrast to normal humans pour out copious amounts of gastric secretion. We were measuring merely the concentration of acid with the method at our disposal; we could not measure total volume output. It was our impression, however, that the normal subjects we had selected for comparison with the ulcer group, secreted both a total volume as well as a concentration of acid equal to that displayed by the ulcer patients. The lower acid values in the duodenal bulbs of these normal subjects, therefore, suggests at least that ulcer patients have some defect in duodenal bulb neutralization.

Other evidences were found in the course of these studies which indicated that gastric acidity per se was not the sole determinant of the acidity in the duodenal bulb. We feel that one of the most important conditioning factors is the type of food undergoing digestion. This was strikingly demonstrated in dogs fed meals made up of each of the basic foodstuffs.

To repeat, our primary purpose was merely to begin to acquire some body of knowledge concerning the actual trend of events in the duodenal bulb, and our most interesting finding probably was the observation that duodenal ulcer patients suffer not only from hyperacidity and hypersecretion but also from defective duodenal bulb neutralization.

DR. THOMAS L. PATTERSON (Detroit) (closing the discussion): Dr. Palmer mentioned the fact that ulcer pains last in the neighborhood of fifteen to twenty minutes or longer. This is very true. However, our kymograph tracings show that before the severe and prolonged episode of ulcer pain occurs, the patient frequently ex-

periences milder and shorter periods of distress. These are at first intermittent and of short duration and later increase in frequency and in duration ending in a continuous more severe ulcer pain as was shown in Fig. 7, which in this particular case lasted eighteen minutes. Because of limited time and space we could not show many of our other tracings. We have one tracing which records continuous ulcer distress for a period of over two hours, during which time the duodenum exhibited increased tone and incomplete tetanus. In not one of our studies, however, did we find ulcer distress when the duodenum was quiescent. The stomach, however, was either in an active or an inactive phase.

We do not wish to have you go away with the idea that we claim that duodenal motility (or hypermotility) is the only factor which enters into the formation of the sen-

sation of pain in duodenal ulcer. Other factors in relation to the duodenum must be taken into consideration and deserve very careful study. They are: The acid or alkaline concentration of the duodenal juice, the presence or absence of duodenal regurgitation, the normality or abnormality of the pancreatic enzymes and bile that enter the duodenum, the potency of duodenal hormones, etc., etc. We wish to stress our opinion that when an ulcer is present in the duodenum, and the patient experiences ulcer distress, abnormal physiological phenomena occur in the duodenum—not necessarily in the stomach. Our studies on duodenal motility and Captain Berk's studies on duodenal bulb neutralization suggest it very strongly. Abnormal physiological phenomena in the duodenum (when a duodenal ulcer is present) should receive greater attention than heretofore.

## Congenital Anomalies of the Primary Midgut Loop

By

JOSEPH M. MILLER, M.D.\*

and

E. G. WAKEFIELD, M.D.†  
ROCHESTER, MINNESOTA

THE various stages of development whereby the intestinal tract of man is transformed from a straight tube to the usual adult shape and position have been studied elaborately by the anatomist. These studies are of inestimable value to the surgeon and the physician in coping with the problems presented by congenital deviations from the usual pattern. Because of the intricate, yet paradoxically simple, process that the primary midgut loop undergoes in arriving at the normal adult stage, many opportunities for arrested development are present. These accidents of development may be grouped conveniently as (1) partial or total exomphalos or hernia into the umbilical cord, (2) complete or partial persistence of the vitelline duct, (3) anomalies of position or so-called malrotation of the midgut loop, (4) abnormalities resulting from traction bands, (5) inadequate fixation with a resultant narrow mesenteric pedicle permitting torsion to occur, and (6) incomplete peritoneal fusion resulting in defects and apertures in the mesentery.

### GROUP I. CONGENITAL UMBILICAL HERNIA

The simplest of these defects is an umbilical hernia in the newborn in which the first stage of rotation may or may not have occurred. In the 5 mm. embryo the intestinal tube is in the midline with the midgut loop forming nearly a right-angled V, the apex of which is continuous with the vitelline duct. At the 7.5 mm. stage, owing to growth of the intra-abdominal organs and an increasing length of the intestine, the umbilical loop is found in the umbilical cord as a hernia. Such a herniation is a natural consequence of growth, for the abdomen is too small to retain its contents.

Case 1. A seriously ill white infant was brought to the hospital one hour after delivery. The sac of an umbilical hernia had ruptured and part of the small bowel was protruding through the rent. At operation all of large in-

testine and several feet of the small intestine were found in the hernia. Considerable difficulty was experienced in replacement, as the bowel was distended and the mesentery of the large bowel was adherent to the sac. The hernial orifice was repaired with two layers of interrupted linen sutures and cure was effected. The hernia may have been due to the adhesions of the mesentery of the large bowel preventing its usual return into the abdomen.

### GROUP II. DEFECTS OF THE VITELLINE DUCT

Persistence of all or part of the vitelline duct after the return of the midgut loop into the abdomen accounts for the various types of omphalo-intestinal pathologic conditions encountered. Included among these are the patent vitelline duct, cyst of the umbilicus, cyst of the duct, a fibrous cord extending from the umbilicus to the intestine, and Meckel's diverticulum. The latter may be found only during laparotomy for unrelated conditions or it may cause one of several syndromes in the abdomen. Acute inflammation may simulate acute suppurative appendicitis very closely and the two conditions often are differentiated only at operation. In addition the diverticulum may become attached to a coil of small intestine or to the abdominal wall and so form an aperture through which intestine may pass and become strangulated. The diverticulum may be the origin of an intussusception. Heterotopic gastric and pancreatic tissues are rather frequently present in the base of diverticula. Ulceration may cause hemorrhage, leading to a peculiar situation which can be diagnosed only through laparotomy. Illustrative of difficulties associated with some of these particular deviations are the following cases.

Case 2. A two year-old boy was stated to have had a discharging umbilicus for more than a year. Some pain and considerable burning were present about the area where the fistulous tract opened externally. Several severe episodes of bleeding from the umbilical region had been noted.

An indurated, edematous umbilical region was found on

\*Fellow in Surgery, Mayo Foundation.  
†Division of Medicine, Mayo Clinic.  
Submitted June 3, 1942.

examination. The pocket in the umbilicus from which purulent material was coming was first curetted and drained. Later the abdomen was opened, the Meckel's diverticulum and the umbilicus were removed and the wound was closed as if an umbilical hernia were present. A patent omphalomesenteric duct accounted for the symptoms and the patient was afforded complete relief.

Case 3. Recurrent attacks of pain in the right lower quadrant were the chief complaint of a twenty-seven year old woman, who had noted this and other symptoms at irregular intervals since seven years of age. The last bout of discomfort had occurred one and a half years before coming to the clinic.

The results of physical examination were essentially normal but when the abdomen was opened a ready explanation for the patient's difficulty was apparent. A Meckel's diverticulum situated 2 feet (61 cm.) above the ileocecal valve had formed a loop through which the entire cecum and appendix had slipped to cause chronic intestinal obstruction. The diverticulum was 9 inches (23 cm.) long and was attached to the umbilicus, and it was necessary to remove both structures. The diverticulum was patent to its tip where it was attached to the umbilicus. A good result was obtained from operation.

### GROUP III. ANOMALIES OF POSITION

If the umbilical orifice is of sufficient size both the proximal and distal limbs of the umbilical loop may enter the abdomen simultaneously. The proximal limb occupies the right and the distal limb the left half of the abdomen. Therefore the cecum and the ascending colon are present in the left lower part of the abdomen. The middle of the transverse colon is attached to the posterior abdominal wall by the retention band so that the cecum, the ascending colon and part of the transverse colon form one limb of an inverted V loop, with the remainder of the colon forming the distal limb. The ileum enters the cecum from the left side instead of from the right. Owing to this freely movable suspended loop, intermittent intestinal obstruction may occur. Of course, with complete occlusion of the blood supply, gangrene results.

Case 4. A man, aged twenty-four years, whose history has been reported previously, stated that he had had intermittent attacks of abdominal cramps which had occurred since birth. During the first three months of life he had had great difficulty in retaining food and gaining weight and the attending physician seriously considered a diagnosis of congenital hypertrophic pyloric stenosis. About the age of three or four months he began to gain weight and developed normally notwithstanding the frequent bouts of abdominal pain. The attacks were sudden in onset, present in the lower part of the abdomen and cramplike in character, being accompanied by borborygmi, abdominal distention and marked vomiting. The duration of these individual episodes ranged from a few hours to two days. Relief was hastened occasionally through the administration of a large enema. Appendectomy was performed in the course of one of these seizures, and at the time it was noted that the appendix lay in the left half of the abdomen. Subsequently laparotomy was performed again for adhesions.

Except for some evidence of being slightly undernourished, the patient did not present deviations from the normal as far as physical examination was concerned. Roentgenographic study of the colon revealed that the cecum was in the left side of the abdomen.

At operation the total mass of mesentery was found suspended from a mesentery, the latter being attached to the posterior abdominal wall in the region of the ligament of Treitz. The base of the mesenteric attachment extended

a short distance down the left side of the abdomen but the intestine did not have posterior attachments to the right of the midline. This lack of attachment permitted a free rotation of 180 degrees in either direction. The cecum and the transverse and sigmoid portions of the colon were in close approximation and loosely adherent to the small bowel. Both superior mesenteric vessels were unusually enlarged, especially the vein. A Meckel's diverticulum with a wide neck was found 15 inches (38 cm.) proximal to the cecum.

The mesentery to the cecum, ascending and transverse colons was freed from its attachment, and the two proximal segments of the colon were carried across the midline and were then fixed in their usual position by silk sutures. Recovery followed and a roentgenogram of the colon made one month after operation revealed that the transferred segments had remained where they had been placed. Rarely the appendix may be found in the left side of the abdomen and of course a similar explanation is offered for its unusual position.

Case 5. A boy, aged nine years, also previously reported (1), was admitted with a history of severe cramplike pain in the lower part of the abdomen for a period of twenty-four hours. Vomiting, fever and rigidity of the abdominal muscles gave testimony of acute intra-abdominal inflammation, although localization was not definite. With a provisional diagnosis of acute appendicitis, immediate operation was advised. A right muscle splitting incision was made and free turbid fluid was encountered. Although the incision was enlarged, only small intestine was seen. As an anomaly was suspected, the abdomen was opened again close to the midline and an acutely inflamed, gangrenous appendix was found lying over the left pelvic brim. The appendix was removed and although temporary enterostomy was required during the early post-operative period, the patient made an excellent recovery.

### GROUP IV. ABNORMALITIES RESULTING FROM TRACTION BANDS

The paraduodenal hernias form an interesting group of cases whose causation has not been explained satisfactorily. Nine fossae about the duodenum are described, although only the left paraduodenal fossa of Landzert and the mesentericoparietal fossa of Waldeyer are of practical importance. Callander (2) and others accounted for the formation of a left paraduodenal hernia by the belief that the upper jejunum and ileum in their migration to the left superior part of the abdomen invaginate the unsupported avascular region between the root of the mesocolon of the hindgut and the inferior mesenteric vein coursing between the two leaves of that mesentery. The mesocolon then falls to the left and fuses with the primitive posterior parietal peritoneum.

It has seemed to us that a somewhat more plausible uncomplicated explanation upon an embryologic basis might be offered for the creation of a left paraduodenal hernia. That portion of the retention band connected to the ileocecal region persists for a longer period than do the other components of the traction band. As the small intestine is "sucked" back into the abdominal cavity from the umbilical hernia, a trough may be formed between the portion of the traction band proceeding to the ileocecal region and the anlage of the hindgut. The small intestine as it comes back would deepen this trough and form a hernial sac. The small bowel therefore would occupy the site it normally does. However, it is separated from the rest of the contents of the abdominal cavity by a peritoneal sac. The cecum, of course, comes to occupy its usual po-

sition atop the intestinal coils, although separated from them by the reduplicated peritoneum. Further growth and development of the proximal segments of the colon proceed in the usual fashion. Such an explanation is simple and sufficient, and may be worked out readily on an embryologic basis.

Case 6. A forty year-old man stated that he had had intermittent pain in the left portion of his abdomen during a period of four years. Signs of occasional obstruction had been noted for the last two years of this period. Thirteen months before the patient came to the clinic his home physician was able to define a mass to the left of the umbilicus. Tarry stools had been noted.

Physical examination was noncontributory except for an area of tenderness in the region of the left segment of the colon and the palpation of an indefinite mass in the left side of the abdomen. Roentgenographic studies of the stomach and colon did not show anything unusual, and a stasis study revealed that barium was distributed throughout the bowel sixteen hours after its oral administration. It was apparent that some unusual condition was present and a provisional diagnosis of either a diaphragmatic or some other type of internal hernia was made.

On exploratory laparotomy a very definite hernial opening was found at the duodenojejunal juncture underneath the ligament of Treitz. The aperture was several inches long and after reduction of the hernia, the orifice was obliterated by suture. As is usually the case, when one congenital anomaly is found another also may be present. This proved to be true here, as in a previous case, for a Meckel's diverticulum was found and removed. The patient reported an excellent result from the operative procedure. It was apparent that pressure upon the inferior mesenteric vein and its radicles by the contents of the hernia accounted for the tarry stools that this patient reported.

Andrews (3) explained the occurrence of right paraduodenal hernia on the fundamental basis of "malrotation." When "rotation" of the umbilical loop was incomplete, the cecum would not lie in a superior position but would be found in the left lower quadrant of the abdomen. However, as the cecum "grew" to the right to occupy the position it normally does in the adult, the small intestine present in the right half of the abdomen would be imprisoned in the lateral leaf of the mesentery of the ascending colon. Fusion of the peritoneal coats of the right segment of the colon with the posterior abdominal wall would complete the formation of the hernia.

Embryologically, such an explanation seems rather involved, for if failure of everything after the "first stage" is present the cecum does not "grow" over to the right lower quadrant as if a tropism were in effect. Again a more plausible account for the formation of right duodenal hernia on the basis of traction bands is suggested. One portion of the traction band proceeds to the duodenojejunal juncture. As the small intestine is "sucked" back into the abdomen, if this portion of the band is persistent, the small intestine may come to lie in a trough formed by the persisting band and the posterior parietal peritoneum. With enlargement of the region, a hernial sac is formed. The small intestine descends to the lower part of the abdomen and the cecum upon entering the abdomen rides above the coils of small intestine in a manner similar to the normal. Subsequent growth of the bowel proceeds in the usual manner. Left paraduodenal hernias occur much more frequently than do their fellows on the right. This may be owing to the fact that the portion of the traction band passing to

the ileocecal region persists to a later date and is stronger than the remaining components of the band.

Clinically it should be noted that such internal hernias may exist without symptoms and may be found only upon laparotomy for an unrelated condition. A mild recurrent intestinal obstruction, the result of an area of hyperplastic tuberculosis, was present in the following case in which a right paraduodenal hernia also was found. Masson and McIndoe (4) have reported the details of this case elsewhere.

Case 7. For seventeen years a forty-one year-old Indian had suffered intermittent attacks of mild epigastric pain coming on two to five hours after meals and associated with bloating, belching and occasional attacks of vomiting.

On examination, intestinal borborygmi were quite audible and a loop of distended intestine could be felt occasionally. Roentgenographic studies of the stomach and colon gave normal results. After the administration of a dye, a poorly functioning gall bladder was demonstrated. Medical treatment was instituted but after a period of four months the patient returned. Because of the increased severity of the complaints it was decided to explore the abdominal cavity surgically.

A right "paraduodenal" hernia containing at least three-quarters of the small intestine was found at operation. The sac extended toward the left iliac fossa. After reduction of the hernia, an area of hyperplastic tuberculosis was noted in the lower part of the ileum. The segment of the ileum that contained this was resected and an end-to-end anastomosis performed. An excellent result was obtained.

Traction bands not only may be an influence in producing "paraduodenal" hernias, but may also cause intermittent intestinal obstruction by compression of the bowel from without. Persistent bands causing pressure are found most commonly about the distal portion of the duodenum around the ligament of Treitz and about the middle of the transverse colon, which site is the second point of fixation of the gut to the posterior abdominal wall. In addition, bands may be found compressing portions of the jejunum or ileum but they do not occur quite so commonly as those just mentioned. A consideration of the history offered by patients who have this type of maldevelopment reveals that difficulty has been present for long periods, and in many cases, since birth. It should be emphasized again that other errors in development may accompany the one producing symptoms.

Case 8. Judd and White (5) stated that a nineteen year-old youth came to the clinic with a history of having pain low in the right epigastric region since the age of two years. The attacks of pain occurred at intervals of two to three weeks and would start soon after the ingestion of food. Vomiting afforded relief and the patient learned to control his discomfort by inducing vomiting. His appendix had been removed during one of these bouts. At the time of operation, the surgeon reported that the appendix was in the left side of the abdomen. However, relief was not obtained.

As is quite usual in such cases, little, except some emaciation, was noted on physical examination. Roentgenographic studies of the stomach gave normal results. It seemed that some type of congenital anomaly was the cause of the pain and accordingly operation was advised.

The duodenum was dilated to about three times the usual size and the distal half was covered completely with peritoneum. In addition it possessed a short mesentery. A firm band, 7.5 cm. in width, extended from the root of the mesentery across the duodenojejunal junction and obviously was the cause of the trouble. The attachment

of the mesentery itself was limited to a small area in the region of the second lumbar vertebra. Marked dilatation of the superior mesenteric vein and its branches was seen. Fusion of the peritoneal layers of the proximal segments of the colon to the posterior abdominal peritoneum had failed to occur and the cecum and ascending colon possessed a long mesentery. The obstructing band was severed and in addition a lateral anastomosis between the jejunum and the first loop of ileum was also made. Convalescence was quite satisfactory and an excellent result was obtained.

When the postarterial segment of the primary midgut loop returns to the abdomen first, the results of a so-called malrotation of the umbilical loop 90 degrees in a clockwise direction are seen. Such an arrangement of the bowel is not due to an actual defect in rotation but simply occurs because the distal segment is "sucked" back first. The cecum and ascending colon eventually occupy their usual positions but the relationship to the superior mesenteric axis is reversed. The vessels are anterior to the duodenum but in the cases under discussion the duodenum or the first portion of the jejunum passes under the vessels. This anomaly of itself usually does not produce symptoms. Such an anatomic deviation was noted in the following case in which the high intestinal obstruction was again the result of a persistent traction band.

Case 9. Frequent bouts of vomiting had been noted in a three year-old boy during the first eighteen months of life. During the year prior to admission, episodes of regurgitation occurred every two to four months. During these attacks the parents noticed that the baby would double up, as if abdominal pain and cramps were present.

The results of physical examination were normal. However, while the child was under observation a partial high intestinal obstruction developed and surgical exploration was undertaken. The stomach, duodenum and upper portion of the jejunum were quite distended, but the remainder of the small bowel was collapsed. A mesentery was lacking in the first portion of the jejunum, and about 8 inches (20 cm.) from the ligament of Treitz the jejunum passed under the superior mesenteric vessels. An incarcerating band almost completely obstructed the jejunum at about this point and when this band was cut, the upper part of the bowel began to deflate. The mesentery of the small bowel was longer than usual but the cecum and appendix occupied their usual position. An entero-enteric stoma was made about 10 inches (25 cm.) from the ileocecal valve and a Witzel type of enteric stoma was established just proximal to it. The patient subsequently recovered from the operation and was free from attacks.

#### GROUP V. RESULTS OF INADEQUATE FIXATION

Volvulus of the bowel is due to inadequate fixation, the result either of a short mesenteric attachment of the small bowel or of lack of peritoneal fusion of the postarterial segment. When the condition is acute, surgical intervention is immediately imperative, for gangrene of the bowel rapidly results. Torsion about the duodenocolic isthmus may occur, in which the entire mass of jejunum and ileum and the colon to the middle of the transverse segment are involved, or if fixation of the proximal portion of the large bowel has occurred, the volvulus may involve only the small intestine. In other cases there is involvement of only segments of the small bowel due to persistent traction bands which may serve as an axis for rotation.

The following case illustrates the changes that may be caused by an unusual chronic volvulus of the small intestine.

Case 10. A forty-three year-old man apparently was healthy until six months before admission, when a dull epigastric pain developed. Vomiting occurred occasionally but blood was not noted in either the vomitus or the feces. The patient had lost 73 pounds (33 kg.) during this period.

Like many other patients with congenital anomalies which cause chronic symptoms, this patient presented little on physical examination except marked malnutrition and evidences of vitamin deficiency. Roentgenographic examination of the upper part of the gastro-intestinal tract revealed an obstruction at the level of the lower part of the duodenum or proximal part of the jejunum. Chemical examination of the blood did not disclose significant changes. As the extremely poor physical condition of the patient prevented surgical intervention, he was treated in a supportive manner in the hope that eventually he might be made ready for operation. However, this result was not achieved.

Post-mortem examination of the abdomen was of considerable interest. Three hundred to 400 cc. of straw-colored fluid was present in the peritoneal cavity, and the stomach and most of the duodenum were markedly dilated. A pocket of peritoneum extended under the ascending portion of the duodenum and a portion of the ileum was found in the sac but the latter was removed easily from the pouch. A pendulous mesentery for the small intestine was attached to the posterior abdominal wall only about the origin of the superior mesenteric artery. Chronic volvulus around this axis had produced the symptoms and signs noted. When acute torsion occurs, gangrene of the bowel ensues. The effects are more quickly evidenced than when gangrene does not occur.

Case 11. A fifty-three year-old woman, whose history has also been previously reported (6), suffered torsion of the ileocecal segment four days after cholecystectomy. Cramplike abdominal pain and the presence of a mass in the lower part of the abdomen necessitated abdominal exploration. At this time a markedly distended, apparently gangrenous cecum was found. Torsion amounted to two complete turns in a clockwise direction.

The involved region was exteriorized and at a later date, continuity of the bowel was re-established.

#### GROUP VI. ANOMALIES OWING TO INCOMPLETE PERITONEAL FUSION

Improper fusion of the peritoneal layers of the bowel to the posterior abdominal wall may result in pouches either under the mesentery of the small intestine or under the cecum or ascending colon. Many patients do not have symptoms and the pouch with its hernia is found in the course of surgical procedure for other conditions.

Case 12. Illustrative of the syndrome which may result when incarceration does occur is the case of a thirty-four year-old man who had suffered recurrent attacks of pain in the right lower quadrant. During one of these attacks, laparotomy for a false diagnosis of acute appendicitis revealed a hernia beneath the mesentery of the small bowel in which 12 inches (30 cm.) of ileum was involved. It is interesting to note that a Meckel's diverticulum was found in this case also.

#### SUMMARY

A few of the more important anomalies which the primary midgut loop may present are illustrated by



case histories. It is essential to note that many of the abnormalities which caused symptoms were accompanied by one or more "silent" anomalies. Many of these congenital deviations do not cause symptoms per se, but are discovered only through roentgenographic studies or on laparotomy for an unrelated condition. This statement is especially true of the paraduodenal hernias. Congenital anomalies must be recalled when an explanation for a chronic digestive disorder is sought, especially if the difficulty dates back to birth.

## REFERENCES

1. Mayo, C. H.: Failure of the Colon to Rotate. *Med. Rec.*, 81:401-403, March 2, 1912.
2. Callander, C. L., Rusk, G. Y. and Nemir, Alma: Mechanism, Symptoms and Treatment of Hernia Into the Descending Mesocolon (Left Duodenal Hernia.) *S. G. O.*, 60:1052-1071, June, 1935.
3. Andrews, Edmund: Duodenal Hernia—a Misnomer. *S. G. O.*, 37:740-750, Dec., 1923.
4. Masson, J. C. and McIndoe, A. H.: Right Paraduodenal Hernia and Isolated Hyperplastic Tuberculous Obstruction; Comment and Report of Case Affecting Jejunum and Ileum; Operation and Recovery. *S. G. O.*, 50:29-39, Jan., 1930.
5. Judd, E. S. and White, R. B.: Congenital Anomalies of the Duodenum with Obstruction at the Duodenojejunal Angle. *Ann. Surg.*, 89:1-5, Jan., 1929.
6. Dixon, C. F. and Miller, J. M.: Volvulus of the Cecum; a Post-Operative Complication. *Minnesota Med.*, 23:250-251, April, 1940.

# Effect of Hemicellulose Hydrogels on the Character of the Stool and Bowel Movement

B<sub>II</sub>

RICHARD BAUER, M.D.  
NEW YORK, NEW YORK

**I**N recent years an enormous amount of literature concerning the causes of constipation and its treatment has appeared. No theory concerning the cause of constipation has been generally accepted and consequently many and varied treatments have been advanced. However, what is generally agreed upon is that for the development of a proper peristaltic movement of the colon it is necessary that the colon receives a proper filling. This filling is brought about normally through the indigestible substances of diet—cellulose, hemicellulose and lignin, in other words, the skeleton of the vegetable food components.

It is generally considered that these substances incite the colon to peristaltic movement mechanically and that this mechanical action of the substances is still further increased by their quite remarkable water absorption. Following these ideas, it has become the fashion to recommend a diet rich in cellulose-containing foods to avoid constipation—and consequently a lot of laxatives containing cellulose and hemicellulose have been recommended. They seem to have opened a new approach to the treatment of colonic stasis. The manner in which they operate, however, is open to some question.

Olmstead (1) and co-workers studied the hemicelluloses and established the fact that they do not pass the intestinal tract intact. They are not acted upon by the ferments of the intestines, but are split by the intestinal bacteria, especially the bacterium coli.

According to Olmstead, under certain conditions from 50% to 70% of cellulose and hemicellulose is destroyed. The resulting products are, besides gases like carbon dioxide and hydrogen, volatile fatty acids, especially acetic, butyric and some formic acid. The largest quantity of volatile fatty acids is formed if the food residue contains relatively much hemicellulose (over 30%) less cellulose, and little lignin. The largest increment of stool weight went with the highest amount of volatile fatty acids recovered from the stools. Therefore, Olmsted concluded that the volatile

fatty acids account largely for the laxative effects seen. This agrees with the conclusions of former authors like Bahrdrf, Edelstein, Langstein, Hecht and others (2). The remainder of the residue, which escapes the bacterial action, has been found to be more or less water binding, thus apparently contributing to the laxative action.

In an attempt to decide for ourselves this question, we have used for our studies a product consisting of small granules containing 37.5% hemicellulose, 7% cellulose and the remainder starch, fat, moisture and minerals. Our investigations were as follows:

First: We tried to determine whether hemicellulose mixed with a normal stool produces a noticeable amount of fatty acids. For this a certain amount of stool was mixed with the product and put in an incubator for 36 hours. As a control, the fatty acid content of the same stool was determined when fresh and also after 36 hours in an incubator, without the addition of hemicellulose.

The normal stool contained a certain amount of volatile fatty acids. This amount increased by approximately 50% in 36 hours. Where the hydrogel product was added, the amount of fatty acids was tripled. (Table I)

A rough estimate shows that from 10 Gm. of hemicellulose in 36 hours about 0.3-0.5 Gm., acetic acid may be formed, if we count all fatty acid formed as acetic acid. It may be mentioned that the same experiment with dried cabbage yielded similar results.

The second experiment was as follows: Six hospitalized patients were put on a diet which contained 1700 calories, half in the form of carbohydrates, or approximately 200 Gm. The stools were examined for volatile fatty acids after the method of Olmsted (3) and his co-workers. The values may be seen in Table II. These patients were then fed 5 Gm. of hemicellulose three times daily with the same diet, and again the volatile fatty acids were determined. In all cases a marked increase of fatty acids was found, similar to that seen with the experiment in the incubator. The increase was relative as well as absolute. On the basis of 10 Gm. of stool, the increase was moderate. Since,

From the Research Department of the Manhattan General Hospital, New York, N. Y.  
The author wishes to express his appreciation to Michael Maiese, B.S., for his valuable assistance.  
Submitted June 12, 1942.



TABLE I

*Comparison of volatile fatty acid content in digestion of hemicellulose with stool in incubator, and without hemicellulose*

| Amount Stool in Grams | Amount Hemicellulose in Grams | Hours in Incubator 37° C. | Volatile Fatty Acid Titrated by 0.1N NaOH in CC. | Increase of 0.1N NaOH in CC. | Total Increase Expressed in Terms of Acetic Acid in Grams |
|-----------------------|-------------------------------|---------------------------|--|------------------------------|---|
| 10.0                  | None                          | None                      | 22.9   | —                            | —   |
| 10.0                  | None                          | 36                        | 35.0   | 13.0                         | 0.078   |
| 10.0                  | 6                             | 36                        | 70.0   | 48.0                         | 0.288   |

Table I shows an increase of volatile fatty acids formed in the stool itself by incubation; but there is a greater increase where hemicellulose is added.

however, the quantities of stool were always increased almost 3 to 4 times, i.e., from 100 to 300 to 400 Gm., the absolute increase was considerable (1.4 up to 4.5 gr. acetic acid). (Table II) The stool when tested with litmus never reacted acid.

Third: It interested us to see whether the increase in amount of stool was correlated with an increased water content. The result of our experiments made that seem probable. If hemicellulose is mixed with 5 times its amount of water, the water soon disappears and the hemicellulose swells to a gelatinous mass. Even 10 to 20 times the amount of water is easily absorbed but this naturally takes a longer period of time.

The water content of normal stools varies. It is believed that a solid stool contains 25 per cent of solids. If the content of solids sinks below 20%, the stool is mushy; below 15% it is diarrheic. Without hemicellulose therapy we found that the stools had a 20-25% solid content.

Since the hemicellulose stools showed a semisolid consistency, we expected a dry content of about 18%. Several experiments showed, however, that the stools, despite their semisolid consistency, contained only about 14% solids. With the aid of hemicellulose, the patient eliminates a semisolid stool despite abnormally high water content. This may be explained by the above mentioned ability of hemicellulose to absorb more than 10 times its quantity of water. (See Table III)

A survey of our experiments shows as follows: The product is able to absorb between 10 and 20 times its own weight of water. The product is able to form volatile fatty acids if mixed with stool and incubated. The stools of patients fed 15 Gr. of the product

TABLE II

*Amount of volatile fatty acids distilled from stools*

| Subject | Amount of Stool in Grams | Volatile Fatty Acids Titrated by NaOH 0.1N in CC. | 24 Hour Stool Quantity Showing Increase in Bulk in Grams | Total Amount of Fatty Acids in 24 Hrs. in CC. of 0.1N NaOH | Increase of Fatty Acids in CC. of 0.1N NaOH | Receiving* Hemicellulose Hydrogel Product | Increase of Fatty Acids Expressed in Grams of Pure Acetic Acid |
|---------|--------------------------|---|--|--|---|---|--|
| W       | 10                       | 11.1  | 38   | 42.2   | —   | —   | —  |
| W       | 10                       | 16.6  | 300  | 498  | 455.8                                       | 3 days                                    | 2.73   |
| W       | 10                       | 17.5  | 456  | 798  | 755.8                                       | 5 days                                    | 4.53   |
| W       | 10                       | 16.2  | 278  | 450.4  | 408.2                                       | 12 days                                   | 2.45   |
| N       | 10                       | 14.7  | 116  | 170  | —   | —   | —  |
| N       | 10                       | 10.0  | 430  | 430  | 260   | 3 days                                    | 1.56   |
| N       | 10                       | 26.0  | 137  | 356  | 186   | 6 days                                    | 1.12   |
| T       | 10                       | 8.6   | 105  | 90.3   | —   | —   | —  |
| T       | 10                       | 7.0   | 177  | 123.9  | 33.6  | 4 days                                    | 0.29   |
| T       | 10                       | 14.6  | 584  | 852.6  | 762.3                                       | 7 days                                    | 4.5  |
| B       | 10                       | 10.65   | 70   | 74.5   | —   | —   | —  |
| B       | 10                       | 12.85   | 280  | 359.6  | 255.3                                       | 6 days                                    | 1.71   |
| M       | 10                       | 6.5   | 106  | 68.9   | —   | —   | —  |
| M       | 10                       | 13.5  | 150  | 202.5  | 133.6                                       | 7 days                                    | 0.80   |
| G       | 10                       | 21.2  | 183  | 387.9  | —   | —   | —  |
| G       | 10                       | 21.7  | 250  | 542.5  | 154.6                                       | 6 days                                    | 0.93   |

\*Hemicellulose hydrogel product given to subjects in dosages of 15 gms. daily. Table II shows a large increase in bulk, and in volatile fatty acids of stool after administration of the product. The hemicellulose hydrogel product used in this study consisted of 37.5% hemicellulose, 7% cellulose, the remainder being starch, fat, moisture and minerals derived mainly from the epidermal layer of plantago ovata seeds.

daily for some days, showed a relatively higher water content when compared with normal stools of the same consistency. This may be explained by the suggestion that the whole stool mass results from one part of stool with normal waste content plus a certain quantity of hemicellulose having absorbed up to 90% of water. Distillation of stools mixed with the product yielded a higher quantity of fatty acids than normal stools.

The percentage of the increase in volatile fatty acids was moderate (up to 50%.) But due to the high increment in stool weight the absolute increase of volatile fatty acids was rather high (up to 4.5 Gr. acetic acid).

Therefore, we agree with Olmsted and his co-workers that the highest increment in stool weight runs

12-30 Gr. for an adult. Such large quantities were never observed either in our studies or by Olmsted and his co-workers (3).

The above cited authors (2) found only acetic acid to be an active laxative, and not butyric and other acids. By virtue of this fact the active quantity of the total amount of volatile fatty acids appears further reduced.

Finally they attribute a laxative action only to this part of the acid content which remains free in the stools. Our stools seemed to contain little free acid, the reaction to litmus never being acid.

Summarizing, we believe that our findings agree substantially with those of Olmsted and his co-workers. However, regarding the question of the laxative effect of volatile fatty acids, formed out of hemicellulose, further investigations appear desirable.

TABLE III

Determination of dry contents of stools

| Nature of Stools                 | Weight of Stool Used in Grams | Weight of Stool After Drying in Gms. | Dry Contents of Stool |
|----------------------------------|-------------------------------|--------------------------------------|-----------------------|
| Normal (semi-solid)              | 2.2095                        | 0.3992                               | 18.1%                 |
| (semi-solid) Hemicellulose stool | 2.4250                        | 0.3350                               | 13.8%                 |
| (semi-solid) Hemicellulose stool | 2.2668                        | 0.3200                               | 14.1%                 |

Table III shows decreased dry contents (increased water contents) in hemicellulose stools in spite of same consistency.

parallel with the highest increase in volatile fatty acids.

Though it seems logical to attribute the laxative action in part to the increase in stool weight and in part to the presence of volatile fatty acids, in order to reconcile my findings with the results of former investigators (2), attention should be called to a discrepancy between their findings and my own.

The above cited authors (2) mixed volatile fatty acids with the food. Therefore the acids could influence the small intestines, while the volatile fatty acids formed out of the hemicellulose most probably originate mainly in the colon.

The quantity of the acids administered orally by these authors was found effective only if given 0.2-0.5 Gr. per kilogram body weight, which would amount to

## SUMMARY

A study of a typical hemicellulose-hydrogel product revealed:

1. The product absorbed and held between 10 and 20 times its weight in water.
2. The resulting stool was semi-solid in consistency in spite of the fact that it consisted of only 14% of solids.
3. Although the amount of laxative fatty acids found in the stool increased proportionately to the amount of the product ingested, at no time was the amount quantitatively or qualitatively sufficient to correspond to an established effective laxative dose.

## CONCLUSIONS

1. The presence of increased volatile fatty acids elaborated in the colon when hemicellulose-hydrogels are ingested is confirmed.
2. The amounts found do not seem to be sufficient in themselves to cause laxation.
3. Whether or not such a quantity of volatile fatty acids may cause a laxative action, if supported by the water-binding action of the remaining hydrogel can only be determined by further study.

## REFERENCES

1. Williams and Olmsted: *Ann. Int. Med.*, Vol. 10, No. 6, Dec., 1936.
2. *Zeitschrift, für Kinderheilkunde*, 1:139, 1911; 3:322-350, 1912; 11:143, 1914; 4:534, 1912.
3. Olmsted, Sunden, Whitaker, Parker: *J. of Biochemistry*, Vol. LXXXV, No. 1, 1929.

# The Gastro-Intestinal Section---Army General Hospital

By

AUGUSTUS A. HALL, M.D.\*  
ATLANTA, GEORGIA

THE gastro-intestinal section, as recognized today, is one of six sections of the medical service of an Army General Hospital. As a fixed unit of the Army Medical Department it is relatively new. Like other new developments, the history of its evolution is of interest. Kantor (1) has epitomized this so well that I will quote from his paper.

\*Major, Medical Corps, Lawson General Hospital, Atlanta, Georgia.  
Submitted August 5, 1942.

"The first attempt in this direction was made in the summer of 1917 when a committee from the Section of Gastro-Enterology and Proctology, consisting of Drs. Martin Rehfuess, Chairman, Dudley Roberts, D. N. Murray, W. M. Beach and others, suggested to Surgeon-General Gorgas that gastro-enterology should be represented in medico-military practice. As a result of several conferences a Section of Gastro-Enterology was created in the division of internal medicine in the

Surgeon General's office under the direction of Major Seale Harris . . . . Following the World War I there was a reaction against over-specialization but this was effectively controlled by the far-sighted attitude of Charles R. Reynolds, Surgeon-General of the Army. In T O 8-507 July 25, 1940, a Section of Gastro-Enterology was included in the Official Tables of Organization. On December 15, 1940, a gastro-enterologist was authorized as a member of the medical service of Station Hospitals of 800 bed capacity or over."

### ORGANIZATION

The description of the arrangement of the space in the gastro-intestinal section, and all other subjects that follow, are based on my experience as Assistant Chief of the Gastro-Intestinal Section at the Lawson General Hospital organized by the present Chief, Major Donald T. Chamberlin.

I. *Space*—The Lawson General Hospital is the cantonment type and the sections are composed of several ward buildings joined together by enclosed corridors. The gastro-intestinal section is composed of five ward buildings running perpendicularly to the enclosed corridor which in turn connects with the rest of the hospital. There is one Officers' ward and four enlisted mens' wards. The bed capacity consists of 18 Officer beds and 120 enlisted mens' beds. It has been generally estimated that about 10 per cent of all medical cases coming to the hospital are gastro-intestinal. This has been the experience of Major Chamberlin. Each ward has a Ward Officer's Office and a nurse's chart-room and office. Each ward has a mixture of a few private rooms and a large ward. The more serious cases are given the private rooms. The office of the Section Chief is at the head of the Officers' ward and consists of two rooms, one of which is for the use of a secretary and the files. On this Officers' ward is also a small laboratory which serves to make stool examinations, procto-sigmoidoscopies, gastroscopies, and other laboratory work, such as the microscopic study of gastric residuum and bile from biliary drainage. All of the wards have a roomy screened-in porch. Each ward has a diet kitchen. This will be referred to later.

### II. Personnel.

a. *Commissioned*—The commissioned personnel consists of a Section Chief with the rank of Major M.C.; an Assistant-Chief, usually a Captain M.C.; and as many Ward Officers as deemed necessary with the rank of 1st Lt. or Captain M.C.

b. *Enlisted*—The enlisted personnel is furnished from the Hospital Medical Detachment. Non-commissioned officers are assigned as Wardmasters and Section Wardmaster. Other Privates and Privates First Class are assigned as Ward Attendants.

It is interesting to know that with the addition of the Medical Department Technician School, near the hospital, new possibilities open up on the section for training purposes. It is planned to have two of the students from this school from the medical technician division assigned to each ward for training. After a suitable length of time they will be replaced by other new students.

c. *Army Nurse Corps*—Members of the Army Nurse Corps are placed on duty in each ward with one acting as Chief Nurse for the Section.

d. *Civilian*—A few of the Ward Attendants are male civilians. The chefs that operate the kitchens are civilians. The secretary of the Section Chief is a civilian.

### III. Administration.

Administration is carried out as in other Sections. Chain of Command and Channels of Communication are maintained through a message center system and by runner. The Chief of the Gastro-Intestinal Section complies with the orders emanating from the Office of the Chief of the Medical Service. As far as practical the Section is decentralized with the Ward Officer exercising his initiative in the successful operation of his own ward subject to frequent inspections by the Chief of Section.

Ward rounds are made twice a day by the Ward Officer in each ward. The Chief of Section makes ward rounds of the entire section daily. Both the Chief of the Medical Service and the Assistant Chief each make ward rounds once a week accompanied by the staff of section.

Daily sanitary inspection is made by an Officer so designated from the command. An inspection of the section is made once a week by the Chief of the Medical Service. The individual wards are maintained in a state ready for inspection at any time.

### IV. Supply.

a. *Food*—Commissioned Officers eat at the Officers' Mess; Nurses eat at the Nurses' Mess; the enlisted personnel and male civilians eat at the Enlisted Mens' Mess. The civilian female secretary provides her own mess by eating at a nearby exchange.

b. *Medical Supply*—Medical supplies are requisitioned in different ways depending on their classification. Deteriorating types of supply, such as rubber gloves, are requisitioned on a six month estimate of expenditure. Non-expendable items, such as an otoscope, are requisitioned as their need arises. Drugs are ordered direct from the pharmacy on prescription. Narcotics, alcohol, tincture of opium, and whiskey are preserved in a locked cabinet. Frequent audits of these drugs are made from the narcotic register.

c. *Property*—Organic non-expendable property of each ward, such as beds, bed-lights, chairs, kitchen equipment (non-expendable), etc., is charged to the Ward Officer in charge of the ward and he becomes the responsible officer for that property. A monthly audit is executed by a representative from the Medical Supply Office and the Ward Officer once each month. When a Ward Officer is relieved from his duty in charge of a ward the property is transferred to another responsible officer.

d. *Administrative*—The various medical forms, such as 55A, supply records, disposition blanks, etc., are requisitioned from Medical Supply on a one year expendable basis. New forms created by the Section must receive the approval through channels. They are then either sent forward to the Army Printing Department, Washington, or they are reproduced here if they are suitable for mimeography.

e. *Miscellaneous*—Ice is delivered regularly by the quartermaster service. The quartermaster laundry cleans all linen from the wards and there is an automatic in and out check on the ward linen count. The

upkeep and maintainance of the buildings is a responsibility of the quartermaster service.

#### V. Patients.

a. *Admission*—All patients on this gastro-intestinal section are male patients. The source of patients is either from this Command; other hospitals in the service; or convoys—either domestic or foreign. On arrival at this Post patients are taken first to the Receiving and Evacuation Office where they are classified, and the gastro-intestinal cases are sent to this section. Officer patients are admitted to the Officers' ward and enlisted patients are admitted to the enlisted mens' wards. The patient's clinical records from his former station accompany him to this section and are attached to his chart for reference.

When a patient is admitted to the ward, the Ward Officer notes his condition and his admission diagnosis. He then orders the initial treatment for his patient changing these orders if necessary when the complete diagnosis is made.

The gastro-intestinal section also maintains an outpatient service for the personnel of this Post.

b. *Method of Study*—All patients are given a most careful diagnostic study including an adequate gastro-intestinal history, a careful physical examination, adequate laboratory examinations guided by the type of illness presented. Certain routine laboratory examinations are made such as urinalysis, blood count, feces, and gastric analysis. Other methods of examination are selective, such as gastro-intestinal X-ray series, gastroscopy, biliary drainage, sigmoidoscopy or cholecystography.

Consultations are requested, whenever indicated, such as cardiac, dermatological, X-ray, or genito-urinary. All Officer patients must be given a complete consultative examination study. This includes ENT, eye, cardiac, chest X-ray and six foot heart film, dental examination, and blood chemistry.

c. *Army Diagnostic Key*—For the convenience of classification of disease it is necessary to have a table of diagnoses, or a diagnostic key. For this purpose AR 40-1025 is closely followed. For anatomical locations AR 40-1025 is referred to. The original 40-1025 basic classification is not adequate enough from the statistical standpoint and guides for additional information appear after each term.

#### d. *Preparation of a case for the CDD or Disposition Boards.*

When a patient is ready for disposition, the component parts of the clinical record are removed from the chart holder, assembled in the folder file, and fastened together with the fastener provided for that purpose. The patient's name, rank, organization, etc., the designation of the ward, and the date of admission are entered in the space provided for that purpose on the outside of the folder. Form 55A is then completed with the following entries:

- a. Disposition of the case.
- b. Final diagnosis.
- c. The line of duty.
- d. The completed form will be signed by the Ward Officer.

When the above has been accomplished a Disposition Slip (Form No. 26 LGH) is made in single copy and attached to the folder of the clinical record. The completed clinical record in the folder is then sent to the

Chief of the Service and thence through channels to the CDD or Disposition Boards. Enlisted men appear before the CDD Board and the Officer patients appear before the Officers' Disposition Board.

e. *Dietetics*—All patients on the gastro-intestinal section are served their meals in the wards until they become convalescent and are able to tolerate the general mess. No patient is sent back to military duty unless he can tolerate a regular mess.

The various gastro-intestinal diets are assigned to the individual patients according to their needs and the dietetic department supervises the preparation and delivery of the food to the ward kitchens. There the food is warmed if necessary. Miscellaneous articles of diets are prepared and served from the ward kitchen, such as fruit juices, milk and cream, and eggs.

As soon as a patient can tolerate the special mess or a regular mess, he attends the Enlisted or Officers' Mess at the regular mess hour.

f. *Patient Discipline*—Upon admission to the Lawson General Hospital, patients are under the complete jurisdiction of the hospital for administrative and disciplinary purposes. In all matters effecting duty, pay, clothing, passes or furloughs, or disciplinary action, they are under the control of the Commanding Officer, Detachment of Patients. In all matters affecting treatment, they are under the control of the Ward Officer and Chief of Service.

An adequate list of rules for patients appears in the LGH Regulations and must be observed by patients. Minor infractions of the patient regulations can best be handled by the Ward Officer by admonition, deprivation of pass privilege, etc. If major offenses are committed, discipline is meted out by the Commanding Officer, Detachment of Patients.

g. *Consultation Service*—The gastro-intestinal section provides consultation service for other departments of the hospital on patients suspected of having a possible gastro-intestinal condition in addition to their other main diagnosis. These consultations are also often necessary from the standpoint of differential diagnosis. If ambulatory or a wheel-chair case, the patient is brought to the gastro-intestinal section with his complete chart. The chart is reviewed and the consultant then takes additional history, makes suitable physical examination in order to render his opinion. This is recorded on a consultation form. The original is sent back to the ward the patient came from and the copy retained by this section. Besides this type of consultation the gastro-intestinal section also provides special consultations, such as proctosigmoidoscopies, gastroscopies, and diagnostic biliary drainages.

#### VI. *Liaison.*

In planning a gastro-intestinal section, it is well to have it within a short walk from the X-ray department. Gastro-intestinal X-ray study is one of the most important parts of the gastro-intestinal diagnosis. A spirit of cooperation between the gastro-intestinal staff and the X-ray staff is very important to good diagnostic work.

The same can be said for the dietetic department. The diet of this type of patient is a large part of gastro-intestinal treatment and it can readily be seen that a lack of proper liaison between the two services

would be detrimental to the proper treatment of these cases.

Proper cooperation with the general laboratory is important. In many cases the results of a test may need some discussion to correlate the laboratory findings with the clinical picture. The small laboratory on the gastro-intestinal section expedites many laboratory problems. Extra fecal examinations are made when necessary, microscopic study is made of gastric residuum and bile from biliary drainage. Smears can be examined from the lower bowel for parasites, such as amoeba.

#### VII. Special Gastro-Intestinal Examinations.

a. *Gastrosocopy*—Gastrosopies performed at the Lawson General Hospital are by Major Chamberlin, Chief of the Section. This is performed in the Section

laboratory room on a table made for that purpose. The patients are carefully selected for this examination and it is not performed as a routine procedure.

b. *Procto-sigmoidoscopy*—This examination is performed by any of the gastro-intestinal staff in the laboratory. Patients are given a preparation enema an hour or so before.

c. *Diagnostic Biliary Drainage*—All diagnostic biliary drainages are done in a room set apart for this purpose. The Meltzer-Lyon technic is used. This is not a routine procedure and the patients are carefully selected for this examination.

#### BIBLIOGRAPHY

1. Kantor, John L.: "Experience with a Gastro-Intestinal Service in an Army Hospital." *The Military Surgeon*, May, 1920.
2. Lawson General Hospital Regulations, April 1, 1941.

## Infra-Red Photography of the Abdominal Wall

By

EDGAR WAYBURN, M.D.  
SAN FRANCISCO, CALIFORNIA

**INFRA-RED** photography has become a proved method to demonstrate superficial veins of the leg (1); to show concealed varices in ulcers and eczema (2), to demonstrate the shrinkage of varicose veins following injection therapy (3), to diagnose vascular tumors (4), and to study the superficial venous pattern of pregnant women (5, 6).

Jones (7) reported six cases of portal cirrhosis with large collateral veins revealed by infra-red photographs and four cases of livers enlarged from other causes in which no collateral circulation could be demonstrated. Jankelson and Baker (8) considered that the pattern of the superficial veins of the abdomen in cirrhosis of the liver was pathognomonic of this disease although the absence of the characteristic vein pattern was not thought to rule out early cirrhosis. In their experience metastatic carcinoma of the liver, diffuse abdominal carcinomatosis and gumma of the liver showed no increase in superficial veins as demonstrated by infra-red photography.

**Material.** The present series is composed of infra-red photographs of the abdomens of 113 patients. As many different sizes, shapes and disease conditions of the abdomen as could be found were included. The patients included 77 persons with cirrhosis of the liver, one with primary carcinoma of the liver, eight with extensive carcinoma metastases to the liver, one with carcinoma not metastatic to the liver, two with retroperitoneal sarcomas, two with malignant cystadenomas of the ovary, one with Hodgkin's disease of the abdominal glands, one with thrombosis of the portal vein, five with cardiac failure of long standing, three of whom had ascites and edema, one with amyloidosis of the liver, two with tuberculous peritonitis, three with acute hepatitis, and three with pregnancy.

**Methods.** All photographs were taken by Mr. H.

Burnett Armstrong, staff photographer at the San Francisco Hospital, for whose constant cooperation the author is indebted. Kodak infra-red film was used with an exposure of 1 second and a lens aperture of f 8. A Wratten (infra-red) No. 87 filter was placed over the lens. Uniform lighting was secured by two No. 2 photoflood lamps in parabolic metal reflectors placed on each side of the patient at 45 degrees. The film was loaded and developed in total darkness. On most of the patients control photographs were also taken. These were made on ordinary orthochromatic or panchromatic visible light film or on infra-red film with the filter removed and the exposure shortened by 75%.

**Characteristic Infra-Red Pictures.** An infra-red photograph of the normal abdominal wall shows either no veins at all or a system of small vessels extending along the lateral aspect and draining into the groins (Fig. 1). As ascites from any cause arises these lateral veins become larger and more numerous and may extend half way to the umbilicus. They are considered to be collaterals which become engorged from obstruction of the vena cava or one of its branches. Distinct from this is the picture of obstruction of the portal vein, in which are seen vessels arising in the region of the umbilicus and progressing proximally or, infrequently, distally; when ascites develops the lateral veins are likewise constantly visible. The typical picture is found characteristically in cases of cirrhosis of the liver with ascites, in which condition there is a group of small superficial veins spread in an anastomotic pattern over the entire upper central abdomen, extending laterally and connecting with the small veins of the vena caval collateral circulation (Fig. 2-A).

**Significance of Superficial Portal Vein Pattern.** The cases were divided into four groups as follows: Cirrhosis with ascites, cirrhosis without ascites, ascites from causes other than cirrhosis and neither ascites nor cirrhosis. Certain patients had to be eliminated

\*From the Department of Medicine, Stanford University Medical School and the Department of Public Health of the City and County of San Francisco.  
Submitted July 14, 1942.



Fig. 1. Infra-red photograph of normal abdomen demonstrating small lateral veins.

from this classification. These included one woman whose superficial veins were clearly demonstrated over the entire body but less prominently over the abdomen than over the chest or arms. There were three cases of pregnancy in whom a typical superficial venous pattern for this condition was evident; this was most marked over the breasts and sternal region, extending secondarily to the upper abdomen. There were two cases of local venous obstruction in which the obstructed veins were clearly outlined. The results of the other photographs are shown in Table I.

TABLE I

*Superficial venous pattern as revealed by infra-red photography in different types of cases*

|                              | Cirrhosis<br>with<br>Ascites | Cirrhosis<br>Without<br>Ascites | Ascites<br>Without<br>Cirrhosis | Neither<br>Ascites Nor<br>Cirrhosis |
|------------------------------|------------------------------|---------------------------------|---------------------------------|-------------------------------------|
| Venous<br>pattern<br>present | 59                           | 12                              | 13                              | 1                                   |
| Venous<br>pattern<br>absent  | 0                            | 6                               | 7                               | 9                                   |
| Total                        | 59                           | 18                              | 20                              | 10                                  |

The anastomotic pattern was most constantly and typically shown in patients in the ascitic stage of cirrhosis. In such cases there is constantly an increased pressure in the portal circulation. The one case of portal thrombosis in our collection had no cirrhosis but demonstrated the typical small vein anastomotic pattern which has been said to be characteristic of the latter disease (Fig. 3). Among the 18

cases of cirrhosis without ascites six did not show superficial venous anastomosis and some of the 12 which did demonstrated few veins; this phenomenon is probably dependent on the amount of portal hypertension present.

There were 20 cases of ascites without cirrhosis, including tuberculous peritonitis, carcinoma primary in the liver, carcinoma secondary in the liver, Hodgkin's disease, cardiac failure, cystadenoma of the ovary and retroperitoneal sarcoma. In eight of these cases autopsies were performed. In one instance there was a thrombosis of the mesenteric vein but evidences of portal thrombi usually were lacking. Among the 20 cases, 13 revealed a superficial portal vein collateral circulation, while seven showed none.

Ten cases without ascites or cirrhosis were included. They included three instances of acute hepatitis, two of hypertensive heart disease, one of generalized arteriosclerosis, two of carcinoma with metastases to the liver, and one of hemorrhoids. None demonstrated any superficial venous pattern. One obese woman with a protruberant abdomen who was thought to have ascites, demonstrated a superficial venous pattern compatible with portal hypertension but at operation was found to have no fluid in the abdomen and no lesion except a fairly small fibromyoma of the uterus.

*Role of Abdominal Distension.* The question of the importance of distention of the abdomen per se has been examined. Infra-red photographs were taken before and after abdominal paracenteses. In a case of ascites secondary to mitral stenosis all veins disappeared after removal of the fluid. In one case of cirrhosis in which the abdomen was drained of fluid a



Fig. 2A. Infra-red photograph of abdomen of patient with cirrhosis of the liver demonstrating portal collateral circulation.





Fig. 2B. Visible light photograph of patient shown 2A.

few small veins only were observed, in two others not as completely drained the collateral circulation was practically unchanged. One patient who had had a portal thrombosis two years before with later recanalization and no fluid in the abdomen at the time of the picture, showed no veins. The abdomen of one patient who had cirrhosis but no ascites demonstrated a well developed portal collateral circulation a year before she returned to the hospital with ascites; a film taken at the latter date was very similar to the first film.

*Comment:* From the clinical aspect the demonstration of the anastomotic pattern of superficial veins over the epigastrium may be regarded as evidence of increased pressure in the portal vein system. It reaches its highest degree of accuracy in cases of cirrhosis of the liver but it is not specific for this disease. In only a little over half the cases wherein infra-red films revealed abnormal veins were the veins noted clinically. In many other cases the film emphasized the clinical observation. Visible light films of the



Fig. 3. Infra-red photograph of abdomen of patient with portal thrombosis and ascites.

abdomen revealed less than the naked eye (Fig. 2-B). In eight out of 14 cases in which spot films were taken radiography failed to demonstrate esophageal varices. The demonstration of a superficial portal vein collateral circulation in the abdominal wall in disease conditions other than cirrhosis deserves emphasis. Portal hypertension occurs more commonly than is ordinarily supposed. It may arise as the result of obstruction in the liver itself, from fibrosis or tumor with consequent distortion of the small veins, as the result of thrombosis of the portal vein, or as the result of external pressure from a tumor mass.

#### SUMMARY AND CONCLUSIONS

(1) Infra-red photography demonstrates superficial veins in the abdominal wall better than the unaided eye or visible light films. The portal vein collateral circulation usually appears in the epigastrium, arising above the umbilicus and flowing cephalad, occasionally below the umbilicus and draining caudad.

(2) Such collateral circulation is the result of increased pressure in the portal vein.

(3) It is characteristic of cirrhosis with ascites, but may appear in other conditions with portal hypertension. It may be present or absent in cirrhosis without ascites. As a corollary it may be stated that increased pressure in the portal vein occurs more commonly than is usually supposed.

I am grateful for the assistance of Drs. Burton Adams and Sadie D. Patek.

#### REFERENCES

1. Barker, N. W.: Demonstration of Superficial Veins by Infra-Red Photography. *Proc. Staff Meet., Mayo Clinic.*, 9:68, Jan. 31, 1934.
2. Haxthausen, H.: Infra-Red Photography of Subcutaneous Veins: Demonstration of Concealed Varices in Ulcer and Eczema of the Leg. *Brit. J. of Derm.*, 45:506, Dec., 1933.
3. Wilson, E. E.: The Changes in Infra-Red Photographs Taken During the Treatment of Varicose Veins. *Am. J. Surg.*, 37:479, Sept., 1937.
4. Ronchese, F.: Infra-Red Photography in the Diagnosis of Vascular Tumors. *Am. J. Surg.*, 37:475, Sept., 1937.
5. Massopust, L. C.: Infra-Red Photographic Study of the Changing Pattern of the Superficial Veins in a Case of Human Pregnancy. *S. G. O.*, 63:56, July, 1934.
6. Gorman, W. A. and Hirschheimer, A.: A Study of the Superficial Venous Pattern in Pregnant and Non-pregnant Women by Infra-Red Photography. *S. G. O.*, 63:54, Jan., 1935.
7. Jones, Edgar: Demonstration of Collateral Venous Circulation in the Abdominal Wall by Means of Infra-Red Photography. *Am. J. Med. Sci.*, 190:478, 1935.
8. Jankelson, I. R. and Baker, H.: Infra-Red Photography of Abdominal Wall in Portal Cirrhosis of Liver. *Am. J. Dig. Dis.*, 5:414, Sept., 1938.

# The Amount of Fat in the Blood After a Meal as Estimated by Counting the Chylomicrons\*

By

RALPH R. COOPER, M.D.

and

HARRY LUSK, M.D.

ANN ARBOR, MICHIGAN

**H**AEMOKONIN particles as seen in the blood by direct light after a meal were first described by Edmunds in 1877 and by Mueller in 1896. They may be divided into two groups—the chylomicrons, in which we are interested in this paper, and which come from the chyle, and lipomicrons, which are derived from the fat depots. In 1908, Raehlmann studied these granules and thought that they were from disintegrated white blood cells. It has since been shown, however, that the granules from white cells do not have Brownian motion, and the chylomicrons do (2).

Neuman, in 1907, suggested that the particles might be fat particles from ingested food. He also suggested that they might be protein, contaminants from the skin, or parasites.

Gage and Fish studied the larger particles in 1924 and decided that they were probably fat. Elkes et al did not believe that he had sufficient basis for this decision.

McDonagh and Peters suggest that they are protein. Cunningham and Peters showed that the bright particles were fat but that the dull particles might be protein.

It is difficult to determine the exact nature of the particles because extraction with any of the fat solvents will upset the colloidal stricture of the serum and cause disappearance of the particles. Until further evidence is available, Frazer et al prefer to think that the dull particles are merely smaller editions of the bright particles. Precipitation with half saturation of ammonium sulfate causes a decrease in particle movement. Full saturation causes an increase in particles.

The particles become immobile at a pH of 5.3. Above and below this pH there is immobility, with precipitation of the particles at a pH of 1. This action can be explained by assuming that there is a layer of globulin adsorbed to the particles. The action of enzymes and filtrates have added nothing. The particles rise to the top in high speed centrifugation. Electrophoresis shows that the particles are negatively charged, as are fat particles in emulsion.

Analyses on venous blood show a parallel between the neutral fat content and these particles. There is no definite relationship between these chylomicrons and cholesterol phospholipids, or protein.

The particles vary in size from one-third to one micron for the bright particles, down to 35 millimicra for the dull particles.

Elkes, Frazer and Stewart (1) believe that the preponderance of evidence points to the particles being

neutral fat, but believe that there may be a layer of adsorbed globulin at the oil-water interface.

Frazer and Stewart (3) found that normally the post-prandial chylomicrograph rose to 150 chylomicrons per field, but that there may be a higher rise in a fat person. The curve may be decreased by feeding lipase and they suggest that there may be more lipolysis in the thin than in the fat individual. According to Frazer's partition theory of fat absorption, there is less lipolysis in the fat subject, and therefore more fat in the peripheral blood, on its way to the fat depots. In the thin person, however, more fat passes to the liver by the portal vein, and less is stored. They

TABLE II

Normals:

Peak at 1½ hours in 2  
Peak at 2 hours in 8  
Peak at 2½ hours in 2

Average height of peak 137.9 chylomicrons per field

Ulcerative Colitis, Untreated:

Peak at 1 hour in 1  
Peak at 1½ hours in 1  
Peak at 2 hours in 1  
Peak at 2½ hours in 1

Average height of peak 47.5 chylomicrons per field

Ulcerative Colitis plus Surgery:

Peak at 2 hours in 1  
Peak at 2½ hours in 2

Average height of peak 150 chylomicrons per field

Pregnancy, with Vomiting:

Peak at 1 hour in 1  
Peak at 2 hours in 3

Average height of peak 41.25 chylomicrons per field

found that the normal curve rose to 125 to 175 particles and the peak occurred in 1½ to 2½ hours after a standard test meal.

They listed the advantages of their method over actual analyses of the blood fat as follows: The changes occur so rapidly that serial observations are necessary. This is difficult in analyzing for blood fat both because of the amount of blood needed and the length of time taken in the analysis. There is a marked difference between the fat content of capillary and venous blood. The former is supposed to be more accurate and is utilized in this procedure. The information obtained by this method is thought by these authors to be more complete and probably just as accurate as that obtained by chemical analysis.

\*From the Departments of Internal Medicine and Gynecology, University of Michigan Medical School, Ann Arbor, Michigan.  
Submitted June 20, 1942.

They believe that any displacement to the left in the curve (as indicated by any rise in the first hour) was due to previously eaten fat. Displacement to the right they believed was due to delayed emptying time of the stomach which might be caused by eating too much fat in the meal. In the usual test meal, the lipemia was over in  $4\frac{1}{2}$  hours, but if larger amounts were fed, the peak was delayed, and the lipemia lasted 6 hours or longer.

We have modified slightly the technique as described by Frazer and Stewart (2). We fed a test meal which was the same as theirs: 60 grams of toast, 30 grams of butter, and one cup of tea, containing 60 cc. of whole milk. This is fed 15 minutes after a fasting blood sample is taken, and the patient is told to consume the whole meal in five minutes. We dropped the first half-hour sample, and took samples at one hour and then each half-hour until the peak was passed. The specimens can be read immediately, or they may be incubated at  $37^{\circ}\text{C}$ . and all read at one time at the end of the procedure.

curred at 1,  $1\frac{1}{2}$ , 2 and  $2\frac{1}{2}$  hours in the four patients seen. The average height was 48, and the range was from 20 to 80 or 85 chylomicrons. In those patients who had had ileostomy or ileosigmoidostomy for ulcerative colitis, the peak in one was at 2 hours and two at  $2\frac{1}{2}$  hours. The average height was 150 and the range 100 to 175.

In obstructive jaundice, the curves never rose above a normal fasting level.

In vomiting of pregnancy, the peak occurred in one hour in one case and at 2 hours in three cases. The average height was 41 chylomicrons per field, and the maximum height 60 chylomicrons per field.

In the one case of diarrhea of unknown etiology, the curve was below slightly the normal range. This patient was later given 50 cc. of olive oil, of which 75% passed out in the stool as neutral fat. The case of questionable pancreatitis also showed a low curve and a delay in the peak. We are not prepared to say whether these changes are significant.

We believe there is suggestive evidence in these

TABLE I  
*Average numbers of chylomicrons in a field at intervals after a standard meal*

|                                   | Fast. | $\frac{1}{2}$ Hr. | 1 Hr. | $1\frac{1}{2}$ Hrs. | 2 Hrs. | $2\frac{1}{2}$ Hrs. | 3 Hrs. | $3\frac{1}{2}$ Hrs. | 4 Hrs. |
|-----------------------------------|-------|-------------------|-------|---------------------|--------|---------------------|--------|---------------------|--------|
| 12 Normals                        | 3.6   | 16.1              | 34.0  | 96.0                | 117.0  | 75.0                | 75.2   |                     |        |
| 4 Ulcerative colitis              | 0.7   | 12.5              | 35.0  | 36.3                | 32.5   | 22.7                | 9.0    | 12.3                |        |
| 3 Ulcerative colitis with surgery | 2.0   | 9.3               | 18.3  | 55.0                | 100.0  | 118.3               | 115.0  | 50.0                |        |
| 2 Obstructive jaundice            | 1.5   | 0                 | 3.0   | 0.5                 | 6.2    | 2.0                 | 4.5    | 0                   |        |
| 4 Vomiting of pregnancy           | 0     | 1.0               | 13.7  | 15.2                | 29.3   | 2.0                 | 0      |                     |        |
| 1 Diarrhea of unknown etiology    | 10.0  | 1.0               | 4.5   | 50.0                | 60.0   | 75.0                | 50.0   |                     |        |
| 1 ? Pancreatitis                  | 1.0   | 25.0              | 25.0  | 35.0                | 35.0   | 45.0                | 50.0   | 1.0                 | 1.0    |

The blood is collected in a capillary glass tube, and one end sealed by flame, using a small blow pipe. The clot is loosened with a fine glass thread, and the specimen centrifuged at moderate speed for approximately five minutes. The serum is then placed on a slide which has been cleaned with bon ami and blown free of dust, and covered with a similarly cleaned cover slip. This is examined by darkfield. We used a 2.0 mm. oil immersion lens, and a 12.5x ocular with a stop  $1/16$  inch square. Several fields were counted in each case, and an average taken. Only the bright particles with Brownian motion were counted.

The accompanying charts indicate our results in 28 patients.

#### DISCUSSION

We realize that our patients are too few in number to allow definite conclusions to be drawn. Our curves on normal individuals parallel well the curves of Frazer et al. The average height of our curves was 138 particles, and the range was 90 to 200. The height of the curve occurred in 2 hours in eight of the patients, and at  $1\frac{1}{2}$  and  $2\frac{1}{2}$  hours in two patients each. In the ulcerative colitis patients the peak oc-

charts that the absorption of fat may be disturbed in ulcerative colitis and vomiting of pregnancy, and further that surgery may tend to correct this absorption in the ulcerative colitis patients. The curve seen in cases of obstructive jaundice (both proven at operation to be complete obstruction due to carcinoma of the head of the pancreas) we believe tends to confirm the belief that the particles seen are fat.

#### CONCLUSIONS

1. The method described by Elkes, Frazer and Stewart for the study of the absorption of fat has been redescribed.

2. The normal values given by them have been confirmed.

3. Suggestive evidence is offered that further study may reveal abnormalities of the absorption of fat in certain diseases.

#### REFERENCES

1. Elkes, J. J., Frazer, C. A. and Stewart, H. C.: The Composition of Particles Seen in Normal Human Blood Under Dark Ground Illumination. *J. Physiol.*, 95:68, 1938.
2. Frazer, A. C. and Stewart, H. C.: Chylomicrograph Technique. *J. Physiol.*, 95:21, 1939.
3. Frazer, A. C. and Stewart, H. C.: Interpretation of the Normal Chylomicrograph. *J. Physiol.*, 95:23, 1939.

# Complete Biliary Obstruction Complicating Duodenal Ulcer; Perforation of the Ulcer Followed by Immediate Release of the Obstruction

By

SAMUEL LEVINE, M.D.\*

and

GEORGE B. GORDON, M.D.†

BROOKLYN, NEW YORK

**I**N spite of the close anatomical relationship between the duodenum and the common bile duct, inflammation or ulceration of the duodenum is rarely complicated by jaundice.

A review of the American literature by Parks and Fitz (1) revealed that only thirty-five (35) cases of jaundice complicating peptic ulcer have been reported. The rarity of this complication is also reflected by the scarcity of case reports in the foreign literature.

Parks and Fitz (1), described a case of painless obstructive jaundice of short duration in a patient with a duodenal ulcer. The cause of the jaundice was ascribed to hemorrhage. Hall (2) states that "jaundice is not a very rare complication in peptic ulcer." Aaron (3) mentions contraction of the ampulla of Vater as a complication of duodenal ulcer. Eusterman and Balfour (4) state that contraction of the sphincter of Oddi occurs in "an occasional instance of chronic perforated duodenal ulcer."

Friedenwald (5) in a review of 1000 consecutive cases of peptic ulcer, of which 529 were duodenal, makes no mention of jaundice. Emery and Monroe (6), in a similar study of 556 cases, likewise failed to record the occurrence of icterus. Hinton (7) reviewed 287 cases and did not mention jaundice as a complication. Rivers (8), in a study of 191 surgically verified cases of duodenitis, gastritis and gastrojejunitis, with and without ulceration, also failed to record the co-existence of jaundice. Fogelson (9), in reviewing the literature from 1934 to 1936, made no note of the occurrence of jaundice in association with ulcer. Laird (10), found an incidence of 4.8 per cent of peptic ulceration in a series of 250 cases which had undergone cholecystectomy. He did not mention jaundice in this group. Such standard textbooks as those by Crohn (11), Hurst and Stewart (12), Rehfuess (13), and Boas (14), make no reference to jaundice as a complication of peptic ulcer.

The foreign literature contains scattered reports; the earliest case was described by Cruveilhier in 1830. Other early case reports were those by Herzfelder (1856), Budel (1857), Foerster (1861), Trier (1863), Krauss (1864), Hoffman (1868), and Morgan (1876). In every one of these cases the jaundice was caused by obstruction of the biliary passages due to fibrous tissue formation. Rolleston and McNee (15), noted sixteen cases reported by Moynihan. More recent reports are those by Tipriz and Dumont (16), Bengolea and Suarez (17), Carniero (18) and Dussant (19). None of the reported cases were complicated by perforation of the ulcer.

In the American group (1), the age incidence ranged from 20 to 54 years. There were 4 males to 1 female.

## CASE REPORT (Chart Number 1104128)

A. S., a 49 year-old storekeeper, came to the office of one of us (S. L.) on Jan. 11, 1941, with the chief complaints of epigastric pressure, anorexia, asthenia, heartburn, and eructations, of two weeks' duration. There was no actual pain, but the epigastric pressure and heartburn were distressing. These sometimes occurred before meals, and were relieved by food and alkalies. He was occasionally nauseated; there was no vomiting or melena. He had lost 8 pounds during his present illness. Ten days before this visit he was fluoroscoped by another physician, and was told that he had a duodenal ulcer. A modified Sippy diet and alkaline powders were prescribed but no relief was obtained while on this regimen. Accordingly, one week later, he again visited this physician, who now informed the patient that he had liver disease. Ten days prior to this visit he noticed that his urine was dark and the stools were light. He did not complain of pruritus or drowsiness. Jaundice was noted by the physician at the second visit.

The patient had previously been well, apart from occasional heartburn, which was relieved by alkalies. He smoked heavily.

Physical examination revealed a thin, markedly icteric, white male. His pulse rate was 70, temperature and blood pressure were normal. The spleen was not palpable, the liver edge was one finger below the costal margin. The gall bladder was palpable three fingers below the costal margin.

Fluoroscopic and radiographic examination revealed a niche in the duodenal cap, about a quarter of an inch beyond the pylorus.

On January 19, 1941, he was admitted to the Beth-El Hospital. Six days later, while he was receiving an enema, the ulcer perforated, and within three hours a laparotomy was performed. The following findings were noted:

On opening the abdomen there was a gush of thick, bile-stained fluid. A perforation of the first portion of the duodenum, anteriorly, was seen from which this was seeping. The gall bladder was collapsed. No calculi were present. The head of the pancreas was slightly indurated. There was intense edema of the gastro-hepatic omentum. The perforation was repaired.

The patient recovered and the jaundice gradually disappeared.

## DISCUSSION

From what we can gather from the literature, the causes for jaundice complicating duodenal ulcer are hemorrhage, inflammation of the ampulla of Vater, fibrosis involving the sphincter of Oddi, adhesions between the ulcer site and the biliary passages, cholangitis, gall stones and hepatitis.

\*Attending Physician, Beth-El Hospital, Brooklyn, N. Y.

†Clinical Assistant, Beth-El Hospital, Brooklyn, N. Y.

Submitted July 1, 1942.

Why was the perforation of the duodenal ulcer suddenly followed by release of the biliary obstruction and collapse of the overly distended gall bladder? For this we can offer no good explanation. It is possible that the jaundice was caused by edema of the gastro-hepatic omentum, compressing the common bile duct. However, this explanation is far-fetched. Edema is, as a rule, more labile, and could hardly be expected to

give rise to complete obstruction of the common bile duct. Furthermore, the *immediate* release of the obstruction, and the collapse of the gall bladder, which followed the perforation, require an explanation. Edema does not subside so suddenly. All we can say is that the rupture of the ulcer was followed directly by the release of biliary obstruction and therefore, these may be in the nature of cause and effect.

### REFERENCES

1. Parks and Fitz: *Rev. Gastro-Enterol.*, 6:179-186, 1939.
2. Hall: *Med. Record*, 84:566-569, 1913.
3. Aaron: *Dis. of Digest. Organs*, p. 310 (Lee and Febiger) 1917.
4. Eusterman and Balfour: *The Stomach and Duodenum*, p. 188 (Saunders) 1936.
5. Friedenwald: *Trans. Ass'n Am. Phys.*, 27:280-296, 1912.
6. Emery and Monroe: *Arch. Int. Med.*, 43:846-873, 1929.
7. Hinton: *Am. J. Surg.*, 20:102-106, 1933.
8. Rivers: *Ann. Int. Med.*, 4:1265-1281, 1931.
9. Fogelson: *Int. Obst. Surg.*, 65:1-19, 1937.
10. Laird: *New Eng. J. Med.*, 213:764-767, 1935.
11. Crohn: *Affect of the Stomach*, (Saunders), 1927.
12. Hurst and Stewart: *Gast. and Duod. Ulcer*, (Oxford U. Press), 1929.
13. Rehfuess: *The Diagnosis and Treatment of Diseases of the Stomach*, (Saunders), 1927.
14. Boas: *Diagnosis and Therap. der Morbkrankheiten*, 1920.
15. Rolleston and McNee: *Diseases of the Liver, Gall Bladder and Bile Ducts*, p. 58, (Mac Millan), 1929.
16. Tipriz and Dumont: *Echo med. du nord.*, Aug. 30, 1930.
17. Benecolen and Suarez: *Arch. argent do enferm. J. ap. digest y la nutrition*, June, 1932.
18. Carniero: *Rev. Ass'n med. argent.*, Sept. 30, 1937.
19. Dussant: *Dia. med.*, July, 1935.

## Abstracts of Current Literature

FRANKLIN HOLLANDER, Associate Editor in Charge of Abstracts, New York, N. Y.

ALBERT CORNELL, New York, N. Y.  
MAURICE FELDMAN, Baltimore, Md.  
CHARLES A. FLOOD, New York, N. Y.  
M. H. F. FRIEDMAN, Philadelphia, Pa.  
J. DUFFY HANCOCK, Louisville, Ky.  
THOMAS A. JOHNSON, Philadelphia, Pa.  
ALLEN A. JONES, Buffalo, N. Y.  
N. W. JONES, Portland, Ore.  
HENRY H. LERNER, Boston, Mass.  
PHILIP LEVITSKY, Montreal, Can.

JESSIE LOVE, Louisville, Ky.  
FRANZ J. LUST, New York, N. Y.  
IRA A. MANVILLE, Portland, Ore.  
ARTHUR E. MEYER, Brooklyn, N. Y.  
FRANCIS MURPHY, Milwaukee, Wis.  
H. NECHELES, Chicago, Ill.  
FRANK NEUWELT, Gary, Indiana  
SAM OVERSTREET, Louisville, Ky.  
J. F. PESSEL, Trenton, N. J.  
DAVID J. SANDWEISS, Detroit, Mich.

RUDOLF SCHINDLER, Chicago, Ill.  
MICHAEL SHUTKIN, Milwaukee, Wis.  
VIRGIL E. SIMPSON, Louisville, Ky.  
H. J. SIMS, Denver, Colo.  
HENRY TUMEN, Philadelphia, Pa.  
ROBERT TURELL, New York, N. Y.  
EDGAR WAYBURN, San Francisco, Calif.  
JOHN WILLARD, Philadelphia, Pa.  
C. WILNER WIRTS, Philadelphia, Pa.

[Microfilm copies of papers may be obtained from Microfilm Service of the Army Medical Library at 25c for each complete article, not exceeding 25 pages in length—and 10c for each additional 10 pages or fraction thereof. Prepayment is not requested. Remittance may be made with subsequent orders and in such manner as found most convenient. Address—Microfilm Service, Army Medical Library, Washington, D. C.]

### CLINICAL MEDICINE

#### STOMACH

WIRTS, C. W., JR.: *The Importance of Gastroscopy in Differentiating Gastric Lesions*. Penn. Med. J., 45: 807, May, 1942.

This author from an analysis of over 1000 consecutive patients found gastroscopic examination to be a valuable adjunct in verifying Roentgen-ray examination of the intestinal tract. In approximately 10 per cent of this series, gastroscopic examination revealed a gastric vent which was not recognized radiographically. —H. J. Sims.

#### BOWEL

RANKIN, L. M.: *Diverticula of the Duodenum*. Am. J. Roent. Rad. Therapy, 47:584, April, 1942.

Rankin reports an interesting case of a large duodenal diverticulum, in which there was a large calcified gall stone. The duodenal diverticulum was of the peri-ampullary variety. The stone measured about 2 inches in diameter, which was demonstrated in the roentgenographic studies. —Maurice Feldman.

#### LIVER AND GALL BLADDER

NIDMEIER, O. W.: *Obstructive Jaundice*. Can. Med. Ass'n J., 46:466, May, 1942.

Jaundice due to obstruction of the

extra-biliary passages interests both surgeon and internist. The observations of the author are based upon 73 cases. Obviously surgery offers the only possible treatment, yet the mortality is sufficiently high to indicate the need for improvement in the present method for handling such cases. The use of Vitamin K has reduced the mortality of the cases with carcinoma. In the cases due to stone, jaundice and liver damage adversely affect the prognosis. A thorough and careful primary operation is essential to avoid the high mortality of secondary procedures. Delay should be avoided between the onset of the jaundice and the operation and the common duct should be carefully explored for stones.

Hepatic failure caused half the post-operative fatalities. This is considered as evidence of too great postponement of operative procedures. The damaging effect of obstruction of the common bile duct upon the liver is in direct proportion to the degree and duration of the obstruction. Infection is usually present with stone and the changes due to it are added to those due to back-pressure.

The cause of delayed surgery is due to difficulties in diagnosis and the tendency "to wait and see" if the jaundice will not clear up spontaneously in which event the cause may be ascribed to toxic or infective factors. Modern methods of diagnosis

justify a delay of no more than two weeks.

The author shows how to exclude the non-obstructive cases of jaundice. He also discussed the differential diagnosis of obstructive jaundice between carcinoma of the head of the pancreas, carcinoma of the gall bladder and stone in the common duct. Careful pre-operative care is essential. The details are given. The administration of Vitamin K is important. Operation should not be performed until the prothrombin time is normal. Post-operative administration of Vitamin K is also necessary. In those cases where the response to Vitamin K is poor, blood transfusions are indicated.

In those cases where stone is found in the common duct and where infection is also present, prolonged drainage is necessary. McDonald's method of "perfusion" is recommended. If a diagnosis cannot be made in two or three weeks, an exploratory operation is advisable. Even in an inoperable malignant condition, relief from the jaundice and pruritis can be given by a cholecyst-gastrostomy done in two stages—a cholecystomy followed by an anastomosis after the jaundice is cleared. The bile tract should be decompressed slowly after the first stage. The relief afforded these patients throws doubt on the diagnosis of malignancy

# Varices of the Gall Bladder; Associated with a Mucosal Cyst\*

## Report of a Case

By

MAURICE FELDMAN, M.D., JEROME E. GOODMAN, M.D.

and

TOBIAS WEINBERG, M.D.

BALTIMORE, MARYLAND

**V**ARICES of the gall bladder is an extremely rare condition. A perusal of the available literature and text-books revealed no recorded case. The association of varices of the gall bladder with a simple mucosal cyst has not been previously reported. A simple mucosal cyst by itself is a rarity. Bodnar, Martinotti, and Adler each report a case.

### CASE REPORT

A woman, aged 53, was admitted to the Sinai Hospital under the care of Dr. A. L. Hornstein. She had complained for one year of pains in the right upper quadrant and in mid-back. She had had four recent attacks which required morphine for relief. There was some nausea and vomiting during her last attack. There was no history of jaundice. There was some gaseous distention, belching, and persistent epigastric discomfort. The physical examination revealed a suggestive mass in the right upper quadrant. The peripheral vessels were normal. There was no evidence of venous disturbances or varicosities. The blood was normal. Cholecystography revealed an enlarged gall bladder shadow, of good, but uneven density. There were two shallow defects close to the neck of the gall bladder which suggested the presence of neoplasms (Fig. 2 A). In the fundus there was a punched out defect about one centimeter in diameter (Fig. 2 B). The gall bladder contracted following a fat meal. There was no sign of stones. The cholecystographic findings were interpreted as representing benign neoplasms.

At operation a curious and bizarre appearance of the gall bladder was observed. It was crisscrossed by dilated, tortuous, engorged veins which arose in the serosa. Another group of unusual prominent veins were noted hanging loosely from the liver bed like a bunch of grapes, spreading over the gall bladder. The cystic vein was markedly dilated. When the cystic vein was clamped, the dilated veins of the gall bladder collapsed, while those originating in the liver bed remained dilated. The liver was enlarged, extending about four finger-breadths below the costal margin.

The gross appearance of the gall bladder showed the serosal surface wrinkled and glossy. The wall was of average thickness. The fundus showed a small mucosal cyst, measuring approximately one centimeter in diameter. It appeared to be superficial, lying wholly within the mucosa and contained a brownish pink-staining granular material. Within the subserosal tissues adjacent the cyst were several enlarged veins. The remaining mucosal surface was normal. Microscopic study of the gall bladder wall showed diffusely scattered lymphocytes and polymorphonuclears. The mucosa was intact and heaped up into folds. The cyst was lined with normal mucous membrane.

The two groups of veins, the cholecystic and hepatocholecystic veins were well demonstrated in our case. The portal system was apparently not involved as there were no varicosities elsewhere.

The etiology of mucosal cyst of the gall bladder is unknown. It is believed that they originate in Luschka's

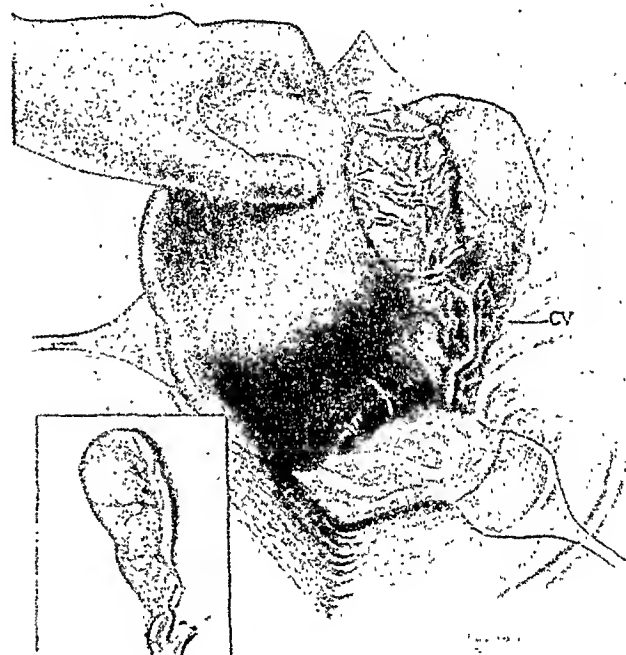


Fig. 1. Drawing of the gall bladder seen at operation, showing the engorged, dilated, varicose veins. The dilated hepatocholecystic veins arising from the liver bed are shown hanging over the gall bladder at arrows HC. Note one of the veins constricting the neck of the gall bladder, which produced the defects shown in the cholecystogram (see Fig. 2). The major cholecystic vein and its branches are shown at arrows ChV. The markedly dilated cystic vein is shown at arrow CV. The small insert drawing illustrates a normal gall bladder, showing the normal caliber and distribution of the veins.

ducts. These duct-like structures are lined with epithelium, but have no connection with the lumen of the gall bladder. According to Bailey they may have connections with the bile ducts and are believed to be remains of aberrant embryonic bile ducts. Kaufmann believes they are eversion of surface epithelium. In Martinotti's case there

\*From the Sinai Hospital, Baltimore, Maryland.  
Submitted July 15, 1942.



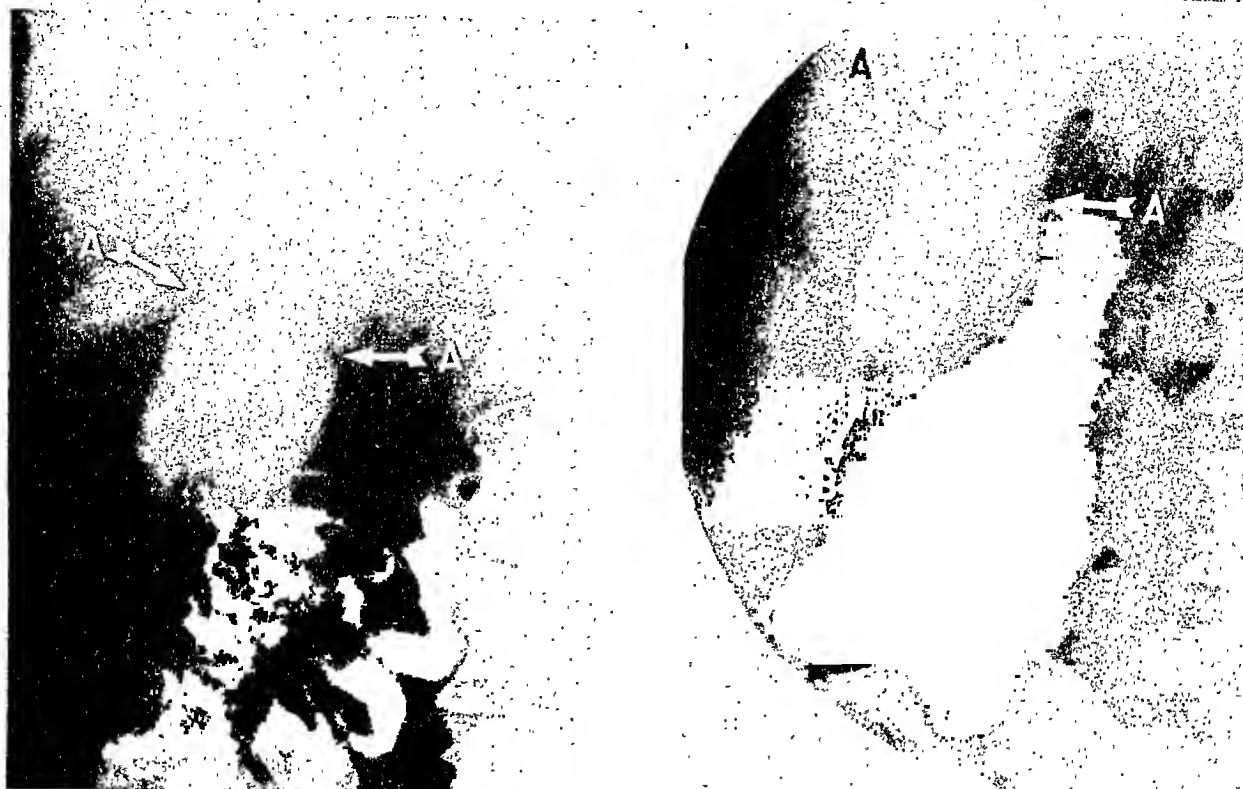


Fig. 2. Cholecystograms of the gall bladder. (a) made in the prone position, and (b) in the left oblique position. The two small defects are well shown along the margins of the neck of the gall bladder at arrows A. The mucosal cyst defect in the fundus of the gall bladder is shown at arrow B. Note the varying density of the gall bladder shadow, with negative areas representing the course of the dilated, engorged veins.

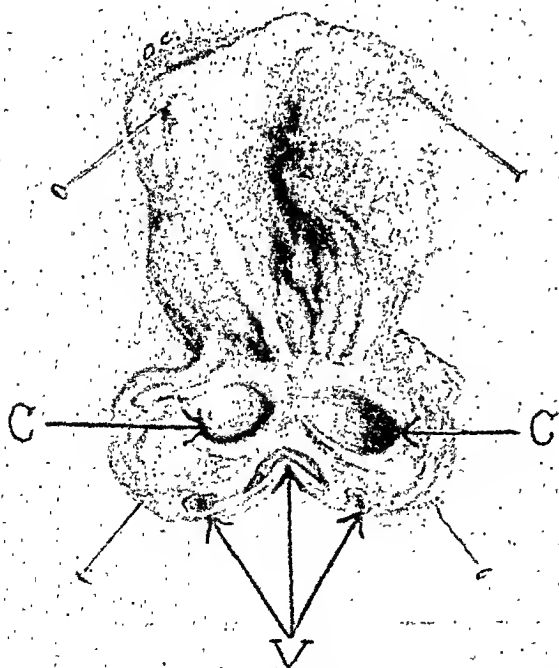


Fig. 3. Drawing of the gross specimen of the opened gall bladder, showing the mucosal cyst at arrow C. The enlarged veins in the subserosa are shown at arrows V.

seemed to be a progressive dilatation of these ducts, forming multiple cysts.

The two small marginal shallow defects situated close to the neck of the gall bladder thought to be neoplasms were not seen when the gall bladder was opened. They were due to constricting veins. An important sign of varices is the presence of different densities in the cholecystogram. Varices then should be considered when the following signs are observed. (1) symmetrical marginal constrictive defects, and (2) varying densities of the cholecystographic shadow, with intervening negative areas corresponding to the course of the veins.

Simple mucosal cysts of the gall bladder give the characteristic roentgen picture of a benign tumor. There are no signs that indicate that the tumor is of cystic nature, unless the mulberry picture of multiple cysts is demonstrated. In the cholecystogram it presents a smooth punched out defect, projecting into the lumen, similar to other benign tumors. The size of the cyst varies from a minute epithelial elevation to the size of a walnut. They are generally small, rarely over one centimeter in diameter. When multiple, an enlarged scalloped gall bladder shadow is shown. Attention is directed to the opacity of the gall bladder, which may be dense, even though there are changes in the vesicle wall.

#### REFERENCES

1. Adler: Reunion libre des chir de Berline, 13 Juillet, 1891. *Compte rendu in Deut. med. Zeitung.*, 60:690, 1891.
2. Bailey's Textbook of Histology. P. E. Smith Ed., 10th Ed., pp. 495. Williams & Wilkins, Baltimore, 1940.
3. Bodnar, L.: Cholecystitis Cystica. *Virchow's Archiv.*, 238:359, 1922.
4. Kaufmann, Edw.: *Pathology*, Vol. 2, pp. 979, 1929. P. Blakiston's Son & Co.
5. Martinotti, G.: Transformazionistica della parete della cistifellea: radiologicamente diagnosticata. *Ann. di radiol. e fis. Med.*, 5:255, 1934.

# A Critical Analysis of 938 Gastroscopic Examinations

By

R. JOHN F. RENSHAW, M.D., GEORGE E. CLARK, JR., M.D.†

and

JOHN R. FORSYTHE, Lt., U.S.A.M.C.

CLEVELAND, OHIO

**T**HIS study is an analysis of 938 consecutive, unselected gastroscopic examinations made upon 842 patients. The review was undertaken in order to determine what, in our experience, had been the value and limitations of gastroscopy; in what type of case had it helped and how had it helped; in what type of case had it failed and why had it failed. The criterion for evaluation and the criticism offered is not only the opinion of the authors, but represents the expression of our colleagues.\*

## MAJOR VALUE

The criterion for considering a gastroscopic examination to be of major value or having made a major contribution to the particular case in consideration

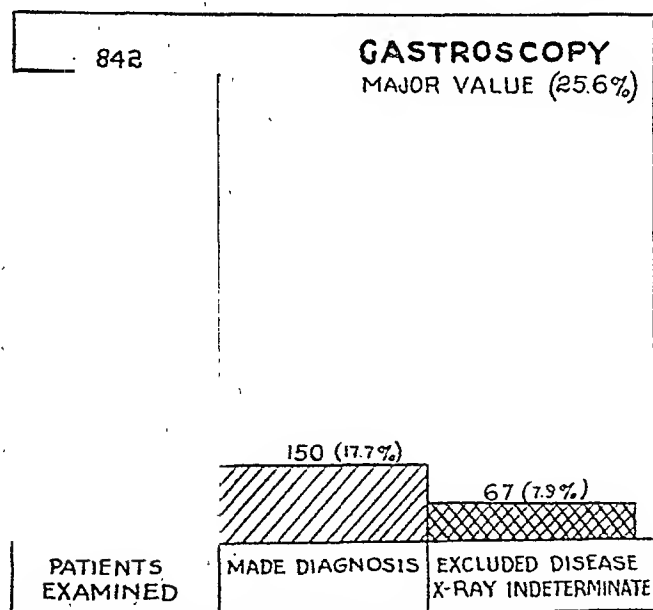


Fig. 1. Major value. Diagnosis made by gastroscopy when other examinations negative or indeterminate.

were the two questions, "Did gastroscopy reveal the diagnosis when the results of all other examinations were negative or indeterminate? Did it seem reasonable to explain the patient's symptoms on the basis of the gastroscopic findings?"

Gastroscopy was considered to have been of major value in 217 patients or 25.6 per cent of our series of 842 (Fig. 1). These 217 patients constituted two groups.

One group included 150 patients in whom the

presence of organic gastric disease was established by gastroscopy. One hundred and twenty-two of the 150 patients in this group had one of the various forms of gastritis which was thought to be the sole or major cause of the patient's symptoms. Eighteen patients had indeterminate roentgenologic reports wherein gastroscopy established the true diagnosis. The remaining 10 patients had gastric ulcers revealed by gastroscopy that had not been revealed by roentgenologic examination.

The second group was made up of 67 patients in whom organic disease was suspected on the basis of indeterminate roentgenologic findings but which was excluded by gastroscopy. Thirty of the 67 cases had indeterminate roentgenologic reports where either carcinoma or ulcer were suspected. The remaining 37 cases had only hypertrophic rugae revealed by roentgenologic examination.

It must be emphasized that negative gastroscopic examinations do not always definitely exclude organic disease due to the blind areas which at times may be quite large. Furthermore, it is not always possible to be certain that the area in question was seen. However, in these 67 cases we were reasonably certain at the time of examination that we had seen the questionable area and had excluded organic disease. In most of these cases the subsequent course of the patient or the results of other examinations done because of a negative gastroscopy proved the findings to be correct. It must be further emphasized that most roentgenologists and gastro-enterologists state that a roentgenologic report of hypertrophic rugae alone is not sufficient evidence to warrant a roentgenologic diagnosis of gastritis. However, because some clinicians still accept the roentgenologist's report of hypertrophic rugae as indicating chronic gastritis, even though the roentgenologist did not mean such an interpretation; gastroscopy was considered to be of value when it excluded gross mucosal evidence of gastritis.

## MINOR VALUE

Gastroscopy was considered to be of minor additional value in 566 cases or 55.4 per cent (Fig. 2). In this group the gastroscopic findings did not alter the patient's major diagnosis, treatment and prognosis. For the most part, the minor contribution was confirmation of the roentgenologic findings. In 238 cases the report of a normal stomach was confirmed by gastroscopy. The pathological condition reported by the roentgenologist was confirmed in 46 cases. In 82 cases a diagnosis of gastritis, or in a few instances, polyps or some other miscellaneous condition was added to major diagnosis.

The last group, wherein gastroscopy was of but minor value, is a miscellaneous one of 100 patients. Seventy-nine of these had no roentgenologic exami-

\*We particularly wish to express our appreciation for the time spent and many helpful suggestions offered by E. N. Collins, Section of Gastro-Enterology, J. C. Root, Lt. Com. U. S. Navy Med. Corps and C. Robert Hughes, Department of Roentgenology.

†Section on Gastro-Intestinal Diseases, Cleveland Clinic.  
Read at the Annual Meeting of the American Gastro-Enterological Association, Atlantic City, N. J., June 8-9, 1942.

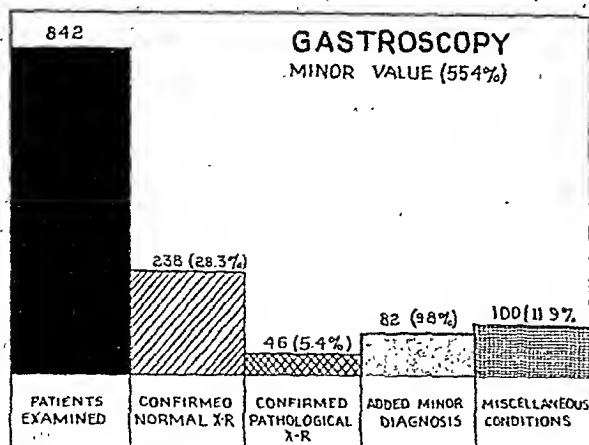


Fig. 2. *Minor value.* Additional information added by gastroscopic examination but major diagnosis and prognosis not greatly affected.

nation of the stomach. These patients all had symptoms suggestive of irritable colon or an unstable vegetative nervous system and the gastroscopic examinations were done largely to exclude gastritis. The gastroscopic findings were normal. In 5 of the 100 cases the gastroscopic diagnosis confirmed the pathological roentgenologic findings demonstrated elsewhere. Ten of the 100 cases had chronic gastritis but since circumstances prevented a complete investigation we cannot be certain that other conditions were not present. Finally, six of the 100 patients previously had had a gastric ulcer demonstrated radiologically but at the time of the progress roentgenologic examination, the stomach was reported normal and by gastroscopy a scar or apparently normal mucosa was found at the site of the previous ulcer.

#### MAJOR LIMITATIONS

It has been stated that gastroscopy was of major value in 25.6 per cent of the 842 patients examined. On the contrary gastroscopy was of no value in only 160 cases or 19 per cent. Fig. 3 indicates the reasons.

One of the important limitations of gastroscopy was the inability to satisfactorily visualize an area in question. There was a total of 75 such instances. Of these there were 57 cases where the roentgenologist

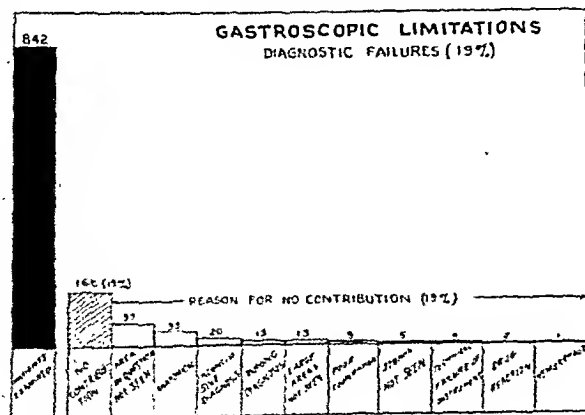


Fig. 3. *Limitations.* Gastroscopic examination not successful or failed to contribute sufficient or correct evidence to case history.

reported either a definite or suspected lesion, but the area in question could not be seen by the gastroscopist. In 13 additional cases not only the area in question could not be seen but also other large areas or the major part of the stomach could not be satisfactorily visualized. Five times the stoma of a gastroenterostomy or gastric resection could not be seen.

The next largest cause of failures was anatomical difficulties. In 35 patients the examination could not be completed because of spasm of the esophagus, acute angulation of the esophagus or angulation of the instrument beyond its useful range.

An inconclusive diagnosis was made in 20 patients. These were the result of the gastroscopist's inability to definitely differentiate between a malignant and benign lesion. The difficulty of differential diagnosis is further shown by the fact that 13 other patients were known to have been incorrectly diagnosed. Poor cooperation or extreme anxiety and apprehension about the procedure prevented completion of the examination in nine cases. Technical failure of the instrument accounted for another four unsuccessful examinations. In two instances the lighting connection

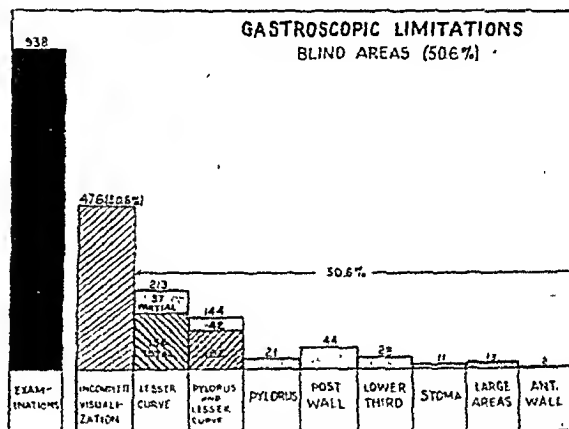


Fig. 4. *Blind areas.* The incidence of the various inconstant blind areas is shown.

broke in the flexible portion after introduction of the instrument into the stomach and in two instances leakage about the objective window and condensation on the window were the causes of inadequate visualization.

It is significant to us that there were five drug reactions in our series of 938 examinations. Two of these five occurred prior to the introduction of the gastroscopist thus preventing the examination. One reaction was due to pontocaine and one to phenobarbital. The last case where gastroscopy did not contribute was in a patient with a duodenal ulcer who developed a hemorrhage while the stomach was being aspirated prior to the introduction of the gastroscopist.

#### BLIND AREAS

Since the greatest limitation of gastroscopy was the failure to visualize the area in question, we were interested to know the size of the constant blind areas and the frequency of the inconstant blind areas. Using fresh cadaver specimens and making moulds of the inflated stomach in situ we believe the constant blind

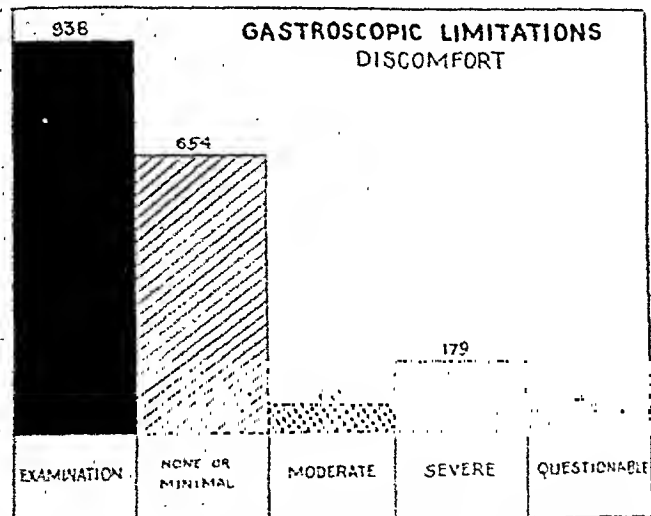


Fig. 5. The degree of distress compared to that of the average patient having an Ewald test meal.

areas at the tip of the instrument, along the posterior wall and in the upper parts of the stomach, are probably larger than most gastroscopists or clinicians realize. The inconstant blind areas and the frequency of their occurrence are shown in Fig. 4. It is significant that in 50 per cent of all examinations or 476 times, certain areas could not be visualized.

In 213 cases the lesser curvature of the antrum could not be seen, 144 times both the pylorus and lesser curvature were not seen, and in 21 instances the entire pylorus only was not visualized. In the remaining 98 examinations the following areas were not satisfactorily observed: unusually large area of posterior wall (44 examinations), the entire antrum or lower third of the stomach (28 examinations), the stoma (11 examinations), and all or large parts of the anterior wall of the body (2 examinations).

#### OTHER LIMITATIONS

The amount of distress suffered by the patient was but a minor limitation (Fig. 5). Compared to the amount of distress indicated by the average patient after an Ewald test meal and compared with the experience of one of us who had a gastroscopic examination, we thought the patients in 654 gastroscopic examinations had no more distress than usually suffered as the result of the Ewald test meal. These were classified as none or minimal distress. In 60 instances the distress was more than average and in 45 it was questionable. Severe distress was experienced in 179 examinations. Many of these patients had some degree of esophagitis or pain on swallowing for one to four days after the examination.

Drug reactions are infrequent but potentially serious when they do occur. In our series there were five reactions. Two were unquestionably due to the sodium phenobarbital given hypodermically prior to the examination. One of these patients had an acute but mild intoxication characterized by disorientation and complete loss of memory for approximately eight hours. The other was a more profound reaction characterized by coma and necessitating the use of picrotoxin. Both cases recovered uneventfully. Of the three other reactions two were either hysterical or

mild pontocaine reactions. They occurred in extremely nervous patients and while the reactions may have been hysterical we could not distinguish them from a true pontocaine idiosyncrasy. One of the possible pontocaine reactions exhibited some convulsive features but neither this nor the other two patients suspected of pontocaine reactions required more than a short period of rest and observation. No additional barbiturates were used to counteract the reactions.

Accidents or perforations may occur as indicated by the reports in the literature. In this series of 938 examinations there was, by an examiner other than the authors, one perforation of the posterior pharynx. Recovery was uneventful following the use of sulfonamides.

#### COMPARISON OF GASTROSCOPIC AND ROENTGENOSCOPIC EXAMINATIONS

It is perhaps hazardous to compare two dissimilar methods which are complementary or supplemental and not competitive. However, we wanted to determine the role gastroscopy had played in the original appraisal of the patient's problem. For this purpose we selected 170 cases that had been followed long enough to definitely establish the diagnosis in or which the diagnosis had been proved by operation or autopsy. Only the first gastroscopic and roentgen examinations and ones made at comparable times were considered. These were considered because they largely determine the clinician's choice of therapy and permit prognosis. Fig. 6 sets forth the results of this comparison. The gastroscopic and roentgenologic examinations were in agreement in 109 of the 170 cases. Both methods were wrong in nine instances and both were indeterminate in 14 patients. The roentgenologic examination was correct and gastroscopy indeterminate in 15, while gastroscopy was correct and roentgenoscopy indeterminate in 23 examinations.

Thus it is seen that one method may be indeterminate while the other may establish the diagnosis. This fact emphasizes the statement of other authors that the methods are complementary or supplemental and

#### COMPARISON OF FIRST ROENTGEN AND GASTROSCOPIC EXAMINATIONS

|  | Normal    | Hg Cast. with Normal or Hg Rug | Gast. X-Ray ? Ca or Ulcer | Ulcer    | Ca         | Benign Tumor or Polyp | Stoma Ulcer |             |    |
|--|-----------|--------------------------------|---------------------------|----------|------------|-----------------------|-------------|-------------|----|
| AGREE  | 43<br>(4) | 39<br>(6)                      |                           | 9<br>(3) | 18<br>(16) |                       |             | 109<br>(29) |    |
| X-RAY CORRECT<br>GASTRO-INCORRECT<br>OR INCONCLUSIVE |           |                                |                           | 9<br>(1) | 4<br>(4)   | 1<br>(1)              | 1           | 15<br>(6)   |    |
| GASTRO-CORRECT<br>X-RAY INCORRECT<br>OR INCONCLUSIVE | 4         |                                | 6<br>(1)                  | 5        | 7<br>(4)   | 1<br>(1)              |             | 23<br>(6)   |    |
| BOTH WRONG   | 1         |                                |                           | 3<br>(3) | 5<br>(5)   |                       |             | 9<br>(8)    |    |
| BOTH INCONCLUSIVE                                    |           |                                |                           |          |            |                       |             | 14          | 14 |

Fig. 6. Comparison of roentgen and gastroscopic examinations. The figures in parenthesis indicate cases with surgical or autopsy proof of diagnosis.

that both types of examination are often required to complete a comprehensive diagnostic investigation.

### SUMMARY

1. An analysis of 938 gastroscopic examinations performed upon 842 patients is presented.
2. Gastroscopy was considered to be of value and to have made a significant or major contribution in 217 or 25.6 per cent of the cases.
3. A minor contribution was made in 566 cases or 55.4 per cent.
4. Gastroscopy was a failure in 160 cases or 19 per cent.
5. The greatest cause of failure was the inability to visualize the area in question, the stoma, or large areas of the stomach. Other lesser causes in their order of importance were: anatomical difficulties, inconclusive or wrong diagnoses, poor cooperation, technical failure of the instrument, and drug reactions.

6. The amount of distress suffered was usually not more than that accompanying an Ewald test meal.

### CONCLUSIONS

We are of the opinion that gastroscopy is a valuable adjunct to our diagnostic procedures. There are certain limitations to the method but they do not minimize the value if the clinician fully appreciates the limitations.

On the basis of this review we believe gastroscopy is indicated in the following conditions:

- (a) Persistent chronic abdominal distress where gastric disease is suspected even though there are negative roentgenologic examinations.
- (b) Indeterminate roentgenologic reports or where the roentgen findings are not consistent with the history and clinical features.
- (c) Gastric ulcer.
- (d) Tumors of the stomach except in emaciated persons with obvious clinical and roentgen evidence of carcinoma.

## Gastric Atrophy in Far Advanced Pulmonary Tuberculosis Complicated by Intestinal Tuberculosis\*

By

LEO L. HARDT, M.D., F.A.C.P., MORRIS WEISSMAN, M.D.

and

JOHN S. COULTER, M.D.

CHICAGO, ILLINOIS

**I**N the course of routine study and treatment of nine hundred fifty-eight cases of intestinal tuberculosis of varying severity for the past eight years, it was noted that some of the cases presented exclusively or predominantly gastric manifestations rather than the standard intestinal symptoms described by us in a previous paper, L. L. Hardt, et al (1). In this somewhat special category it was observed that there was a greater incidence of upper abdominal distress, belching and flatulence with a correspondingly reduced frequency of the usual pain localizations and diarrhea episodes. Realizing that the intestinal involvement was, in all likelihood, still in its relatively early development when it is apt to yield upper abdominal reflex manifestations instead of organic changes, it was decided to examine these cases gastroscopically, especially since in a review of one thousand post-mortems previously reported by L. L. Hardt and S. J. Cohen, (2) from the Municipal Tuberculosis Sanitarium,† atrophic gastritis was a frequent finding.

There has been very little work done gastroscopically in patients suffering from pulmonary tuberculosis. A study was made of the changes in the gastric mucosa in one hundred nineteen cases of pulmonary tuberculosis with gastro-intestinal symptoms selected from a group of two hundred and fifty of the cases which we had gastroscopied. Peptic ulcer, malignancies,

gall bladder pathology and tuberculous lesions other than pulmonary and intestinal were eliminated in this group of cases. Of this studied group—fifty-six, or 47.2% were gastroscopically normal, while the remaining sixty-three, or 52.8%, showed definite atrophic changes. An attempt was made to correlate the gastroscopic findings with the pathological findings, both gross and microscopic, to evaluate the symptomatology and laboratory data and to give a preliminary report on the effect of short wave diathermy in the treatment of the atrophic changes observed.

The work of K. Faber, and C. E. Bloch (3), G. E. Konjetzny (4), W. A. Swalm and L. M. Morrison (5), and others, suggest that in atrophic gastritis there is a primary inflammatory reaction of the mucosa, followed by destruction of the glandular structure, resulting in atrophic gastritis. In most instances there appears to be a transition from the superficial gastritis to the later stage of atrophic gastritis; in the latter stage there being a marked destruction of the mucosal glands and a cellular infiltration composed largely of round cells, plasma cells and fibroblasts, and not infrequently a marked increase of connective tissue.

C. M. Jones, E. G. Benedict and A. O. Hampton (6) suggest in their study of the gastric changes in pernicious anemia that much of the gastric atrophy noted in pernicious anemia by various observers represents an atrophy of the mucous membrane due fundamentally to a specific deficiency rather than to a chronic gastritis. They also point out the possibility

\*Aided by grants from the Consul of Physical Therapy of the American Medical Association and the Wisconsin Alumni Research Foundation.

†Municipal Tuberculosis Sanitarium, Chicago, Illinois.

Read at the Annual Meeting of the American Gastro-Enterological Association, Atlantic City, N. J., June 8-9, 1942.

of the reversibility of the mucosal changes characteristic of chronic atrophic gastritis accompanying pernicious anemia in induced remissions.



It is the consensus of opinion, based on a review of the literature, that there is nothing characteristic of the symptomatology of gastritis. There is usually something in the symptomatology, however, that directs the observer to the stomach. R. Schindler and H. M. Murphy (7), analyzed the symptoms in forty-one cases of atrophic gastritis and concluded that the digestive symptoms were rather indefinite. Epigastric discomfort, fullness, belching, poor appetite, nausea, vomiting, general weakness and fatigue were the predominating symptoms. The laboratory data was of little aid. The gastric analysis in these cases corresponds with the findings of K. Faber and C. E. Bloch (3), A. F. Hurst (8), and others; namely, a general lowering of both free and combined hydrochloric acid.

vomiting, belching, flatulence, loss of weight, epigastric distress—gnawing or burning in character, general weakness and fatigue were the predominating symptoms. Bearing in mind that these cases are all complicated by intestinal tuberculosis, a number of them had bowel symptoms—constipation or diarrhea, or constipation alternating with diarrhea.

It is interesting to note (see chart) that there is for practical purposes relatively slight difference in the symptoms between the group that was gastrosco- pically normal and the group in which atrophic changes of the mucosa were noted. In the atrophic group on the whole, loss of appetite, nausea, vomiting, loss of weight, occurs with greater frequency than in the normal group. There is nothing in the clinical history therefore that could lead one to make a posi- tive diagnosis of atrophic gastritis without the aid of a gastroscopic examination.

Value of Clinical Symptoms in the Diagnosis of  
GASTRIC ATROPHY  
in Patients with Far Advanced  
Pulmonary Tuberculosis and Tuberculous Enterocolitis.

| SYMPTOMS                | No. Cases | Percentages | SYMPTOMS             | No. Cases | Percent. |
|-------------------------|-----------|-------------|----------------------|-----------|----------|
| Loss of Appetite        | 30        | 53.5        | Location of Pain     | 1         | 1.7      |
| Acid Eructation         | 26        | 46.4        | R.U.Q.               | 2         | 3.1      |
| Nausea                  | 29        | 46.3        | " L.U.Q.             | 2         | 3.5      |
| Vomiting                | 33        | 58.9        | " Umbilicus          | 6         | 9.4      |
| Belching                | 44        | 68.7        | " Epigastric         | 1         | 1.7      |
| Diarrhea                | 23        | 46.4        | " R.L.Q.             | 9         | 14.1     |
| Constipation            | 38        | 59.3        | " L.L.Q.             | 18        | 32.1     |
| Alternating             | 33        | 59.9        | " Diffuse Abdom.     | 13        | 20.3     |
| Diarrhea & Constipation | 38        | 59.3        | Across Lower         | 10        | 17.8     |
| Loss of Weight          | 12        | 21.4        | " Abdomen            | 9         | 14.1     |
| Flatulence              | 19        | 29.7        | Across Upper         | 4         | 7.1      |
| Character of Pain:      | 10        | 17.8        | " Abdomen            | 6         | 9.4      |
| Gnawing                 | 9         | 14.1        | Relief with Vomiting | 2         | 3.5      |
| " Burning               | 5         | 8.9         | Across Lower         | 8         | 12.5     |
| " Heart-Burn            | 6         | 9.4         | " Abdomen            | 7         | 12.5     |
| " Cramp-Like            | 24        | 42.8        | " Across Upper       | 2         | 3.1      |
| " Sharp                 | 40        | 62.5        | " Abdomen            | 2         | 3.5      |
| " Boring                | 35        | 62.5        | Worse with Eating    | 1         | 1.6      |
| " Stabbing              | 42        | 65.6        | " B.M.               | 3         | 5.3      |
|                         | 6         | 10.7        | " Change of          | 6         | 10.9     |
|                         | 9         | 14.1        | " Position           | 5         | 7.6      |
|                         | 19        | 32.1        | " B.M.               | 2         | 3.5      |
|                         | 5         | 7.9         | " Change of          | 9         | 14.1     |
|                         | 9         | 16.1        | " Position           | 10        | 17.8     |
|                         | 8         | 12.5        | " B.M.               | 1         | 1.6      |
|                         | 13        | 23.2        | " Change of          | 9         | 16.1     |
|                         | 13        | 20.3        | " Position           | 3         | 4.7      |
|                         | 0         | 0           | " B.M.               | 2         | 3.5      |
|                         | 0         | 0           | " Change of          | 1         | 1.6      |
|                         | 6         | 10.7        | " Position           | 4         | 7.1      |
|                         | 10        | 15.6        |                      | 0         | 0        |
|                         | 5         | 8.9         |                      |           |          |
|                         | 9         | 14.1        |                      |           |          |

Key: White  Normal (gastroscopically)  
Black  Atrophy

Our gastroscopic findings in the atrophic group are similar to the many descriptions of atrophic gastritis in the literature. Areas of thin mucosa, gray or greenish-gray in color, frequently associated with a marked diminution in the size of the rugae were seen. In the far advanced picture the blood vessels were readily visualized through the thin mucosa—the stage of gastric atrophy. In the less advanced there were islands of mucosa, watery and edematous in appearance, pink-red to beefy-red in color, with increased high lights, which we denote as the pre-atrophic stage. The usual picture is a combination of the pre-atrophic and atrophic stages. The gastroscopic appearance was quite similar to the gastroscopic picture found in a number of vitamin deficiency cases observed in chronic alcoholism and pellagra.

The symptomatology that led us to advise gastroscopic examination was similar to that described by Schindler. Loss of appetite, acid eructations, nausea,

The routine gastric analysis, using the Ewald test meal as a guide, was done in both the atrophic as well as the normal group. The average total acidity in the atrophic group was 43.3, the average free hydrochloric 23.0, with an average combined acidity of 22.5. In the normal group the average total acidity was 49.2, the average free 26.8, and the average combined acids 25.5. There was a definite tendency to a lowering of the acid values in the atrophic group compatible with the findings of others as mentioned in the literature.

The histological examinations were made on forty-two stomachs that had been immediately removed post-mortem and fixed. The sections for this study were routinely taken from the lesser curvature just proximal to the angulus along the posterior wall. Eleven of our cases showed normal stomachs with a mucosa of normal thickness, scanty interstitial tissue, no cellular infiltration, and long, straight glands composed of



large cells (see Fig.). Eighteen of this group showed *simple atrophy*. The mucosa was thin, the interstitial tissue prominent but free of cellular infiltration. The glands were short, tortuous, and composed of small cells (see slide). Thirteen showed *inflammatory changes*. In them the thin mucosa consisted of short, distorted glands composed of small cells, with round cell, plasma cell and eosinophilic infiltration of the prominent interstitial tissue. Exudate was scanty and occasional (see Fig.).

In all our cases the submucosa and muscularis were normal. Autolysis was exceptional and was characterized by loss of the upper half of the mucosa with poor staining of the remainder except the very deepest portions of the glands. In view of the lack of invasion of the deeper structures of the mucosa by an



Fig. 1. *Atrophic Gastritis*. The mucosa is narrow. The interstitial tissue is prominent and infiltrated with round cells, plasma cells, and eosinophiles. The glands are short, distorted and composed of small cells.

inflammatory process and in view of the large percentage of simple atrophies without inflammatory change, we are inclined to believe in this group at least that the gastric atrophy is primary and the inflammatory changes are secondary.

In spite of the fact that all these patients were on a high vitamin smooth diet, reinforced with Brewer's Yeast Tablets, 20,000 units of Vitamin A, 400 units of Vitamin D in the form of irradiated milk or 2,000 units of Vitamin D concentrate, 52.8% showed varying stages of gastric atrophy. Frequent high temperatures and sweating are common occurrences in this group of cases. It was pointed out by one of us in a previous communication, L. L. Hardt and E. U. Still (9), that there was an appreciable loss of Vitamin B and C in the sweat. Therefore it would seem that there should

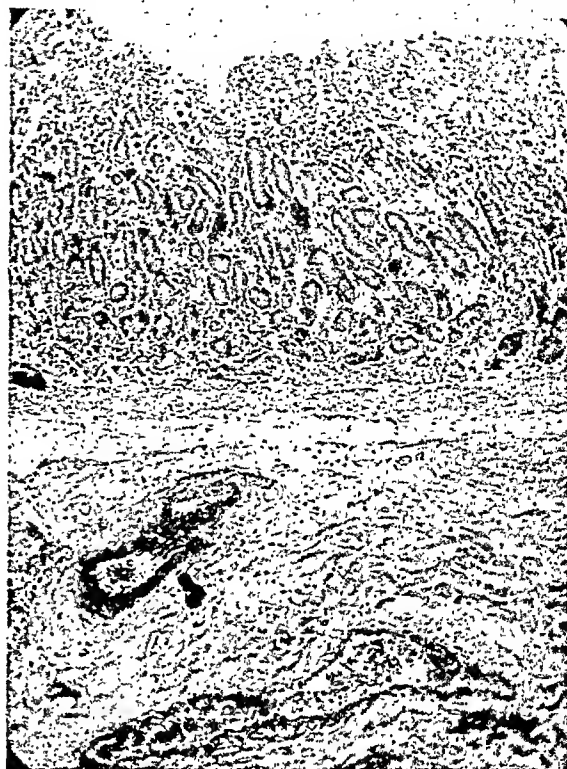


Fig. 2. *Simple Atrophy*. The mucosa is narrow. The interstitial tissue is prominent. The glands are short, tortuous, and composed of small cells. There is no cellular infiltration.

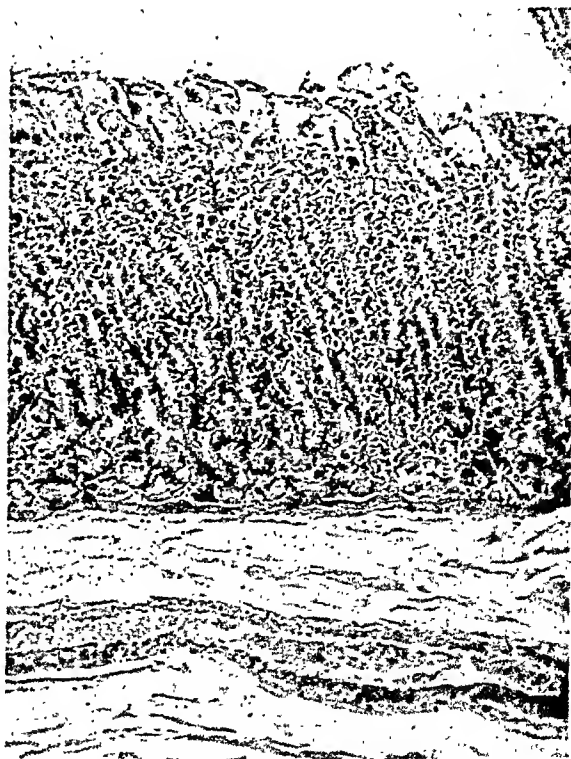


Fig. 3. *Normal Gastric Wall*. The mucosa is thick. The interstitial connective tissue is very scanty. There is no cellular infiltration. The glands are long, straight and composed of large cells.

be an increase of vitamin intake or a more complete utilization of the vitamins given. Short wave diathermy applied to the abdomen will raise the temperature of the stomach one to two degrees and therefore increase the blood circulation in the stomach. It was believed that by increasing the circulation of the gastro-intestinal tract, its absorbing power would thereby be increased, resulting in a more complete utilization of the vitamins. In this series twenty-five patients were given short wave diathermy by electromagnetic induction to the abdomen for twenty minutes each day. This was continued for a period of six to twelve weeks, when the patients were re-gastroscooped and their symptoms reviewed. In practically every instance there was almost a complete absence of symptoms at the end of six to twelve weeks. Gastroscoopically there was a reversal of the picture varying in degree from normal to moderate preatrophic stages.

Five of the twenty-five either refused to be re-gastroscooped or left the institution and could not be recalled, five had completely returned to normal, five were practically the same as on previous examination, while the remaining ten showed a definite tendency toward reversal to normal.

In conclusion, it is desired to emphasize that (1) atrophic changes in the gastric mucosa is a frequent occurrence in far advanced pulmonary tuberculosis complicated by intestinal tuberculosis; (2) this condition can be diagnosed gastroscoopically; (3) the histopathology indicates primary atrophic changes with secondary inflammatory changes; (4) the results of short wave diathermy to the abdomen indicate that it is a valuable adjunct in the treatment of gastric atrophy.

We wish to thank Dr. Louis Parmacek for his aid in the histological interpretations.

### REFERENCES

1. Hardt, L. L., Weissman, M., Cook, C. E. and Martin, C. L.: Tuberculous Enterocolitis; Diagnostic Data. *Illinois Med. J.*, Sept., 1939.
2. Hardt, L. L. and Cohen, S. J.: The American Review of Tuberculosis, Vol. XLIII, No. 5, May, 1941.
3. Faber, K. and Bloch, C. E.: Ueber die pathologischen Veränderungen am Digestionstractus bei der perniciosen Anämie und über die sogenannte Darmatrophie. *Ztschr. f. klin. Med.*, 10:258, 1894.
4. Konietzky, G. E.: Die Chronische Gastritis des Uleus-magens. *Centralblatt f. Chirurgie*, 50:1026, 1923.
5. Swalm, W. A. and Morrison, L. M.: *Am. J. Dig. Dis.*, 5:391, Oct., 1941.
6. Jones, C. M., Benedict, E. G. and Hampton, A. O.: Variations in the Gastric Mucosa in Pernicious Anemia. *Am. J. Med. Sci.*, 190:596, Nov., 1935.
7. Schindler, R. and Murphy, H. M.: Symptomatology of Chronic Atrophic Gastritis. *Am. J. Dig. Dis.*, 7:7-13, 1940.
8. Hurst, A. F.: Achlorhydria and Achylia Gastrica, and Their Connection with Addison's Anemia—Subacute Combined Degeneration Syndrome and Simple (Non-Addisonian) Achlorhydric Anemia. *Quart. J. Med.*, 1:157, 1932.
9. Hardt, L. L. and Still, E. U.: Proceedings of the Society for Experimental Biology and Medicine, 48:704-707, 1941.

## Gastric Mucosal Changes of Tuberculosis\*

By

DONOVAN C. BROWNE, M.D., GORDON MCHARDY, M.D.

and

CARL WILEN, M.D.

NEW ORLEANS, LOUISIANA

**G**ASTRIC tuberculosis, a rare entity, has defied clinical diagnostic acumen. Broder's critical survey of the literature, subsequent to Coats' presentation of the first proven instance in 1886, revealed 49 authentic and 118 probable cases. His diagnostic criteria eliminate approximately 50 per cent of the published case reports. In 373 acceptable cases appearing prior to 1942, we could find only six authors with any claim to a clinical diagnosis of the entity. (Von Schlesinger, Haudek, Spengler, Pohl, Lapeyre, Pope and Hanganutin). The lack of specific symptomatology, the absence of pathognomonic physical findings and the limitations of roentgenology render the condition more a pathological entity than one of clinical significance. With the advent of gastroscopy, increased diagnostic accuracy would seem inevitable, but there are, as yet, no unusual endoscopy claims.

The actual incidence of tuberculosis of the stomach is best illustrated statistically:

| Authors        | Number Tuberculosis Necropsies | Cases of Gastric Tuberculosis | Percentage |
|----------------|--------------------------------|-------------------------------|------------|
| Good           | 15,165                         | 80                            | 0.52       |
| Sullivan et al | 554                            | 2                             | 0.35       |
| Glaubitt       | 2,237                          | 47                            | 2.00       |
| Simmonds       | 2,360                          | 18                            | 0.76       |

The average incidence in surgical exploratories approximates 0.12 per cent.

The rarity of tuberculous involvement of the stomach is established. It is, therefore, interesting to speculate as to the origin of dyspeptic symptomatology associated with or actually predominating in pulmonary tuberculosis as observed in 92 per cent of cases by Hutchinson and by Fenwick in 83 per cent. Brown's hypothesis "hypersensitivity of the mucosa of the stomach" seems confirmed by the mucosal changes found by Marfan and by Faber on autopsied stomach.

\*From the Department of Medicine, School of Medicine, Tulane University, and the Gastroscopic Service of Charity Hospital, New Orleans, Louisiana.

Read at the Annual Meeting of the American Gastro-Enterological Association, Atlantic City, N. J., June 8-9, 1942.

The gastroscopic observations of Ollerer and Viesca suggest a gastritic basis and they hypothesize an allergic relationship.

### EXPERIMENTAL TUBERCULOUS GASTRITIS

Animal experimentation in the production of gastric tuberculosis, especially those of Montemartin and of Orth, have considered four routes of invasion: 1. Direct mucosal involvement; 2. Extension from extra-gastric lesions; 3. Lymphatic infiltration (retrograde); 4. Hematogenous. Judging from this work, necropsy findings and the conclusions of others, the involvement occurs by mucosal entrance through a broken area or by hematogenous dissemination.

More important, in our opinion, are the types of mucosal change producible in the animal that from actual observation conclusions may be drawn from similar gastroscopic visualizations in man. This formed the basis for our experimental study which, with our endoscopic findings led to our conclusions.

In our experimentation, we gave due appreciation to gastric acidity. The literature reveals tuberculosis is characterized by hypoacidity; that there are numerous case reports of proven gastric tuberculosis with hyperchlorhydria, that normal gastric secretions and hydrochloric acid have no effect on tuberculosis organisms after 12 hour contact. Nevertheless, we injected achlorhydric pouches and those with normal gastric secretions.

The rapid emptying of the stomach has been considered significant, but seems unimportant when the rapidity of emptying of the small bowel, so frequently involved, is appreciated. However, we used static gastric pouches to effect an ideal site.

The resistance of an intact gastric mucosa being recognized, the mucosa was traumatized in each instance.

Although it is difficult to explain the lymphatic theory of invasion, because of the necessity for this to be retrograde and the uniform absence of muscularis involvement, we nevertheless considered this because of the predominance of gastric lymphatics in the pyloric segment and, therefore, directed all our efforts toward this site.

Hematogenous dissemination was given every opportunity using the gastropiploic artery with distal ligation.

The preparation used was an emulsion of a culture from a patient dying with advanced disseminated tuberculosis, the virulence of which was unquestionable.

The dog was used as our experimental animal for it is well established that the canine is the most suitable subject as exemplified in Day's summarization of experimental tuberculosis and, furthermore, that it lends itself to gastroscopy.

Our results showed: (See Charts I and II).

1. The cardiac achylic pouch did not develop any significant lesion.

2. The Fundal pouch (free acid present) did not develop any pathology.

3. In the pyloric pouch two methods produced significant histologic changes:

A. Submucosal implantation into a non-sensitized area produced a tumefaction with a necrotic mound which sluffed away leaving a superficial ulceration which healed over with intact mucosa covering extensive submucosal infiltration of lymphoid and plasma

cells with numerous leukocytes. There was no epitheloid response, but acid fast organisms were readily demonstrated. This unusual exudative response may be of the type described by Lewis.

B. Hematogenous methods resulted in proliferative epitheloid changes in the submucosa and early exudative response and adjacent nodes.

### PATHOLOGIC TUBERCULOSIS GASTRITIS

To establish a positive diagnosis of gastric tuberculosis, Broder required the pathological picture of

#### Chart I Methods Used (Associated With Local Trauma)

##### 1 Direct Contact

##### 2 Injection:

- |                           |                                    |
|---------------------------|------------------------------------|
| A. Submucosal             | { Injection<br>And<br>Implantation |
| B. Muscularis             |                                    |
| C. Subserosal             |                                    |
| D. Perigastric Lymphatics |                                    |

##### 3 Hematogenous:

(Vessels Ligated Distally To Prevent Dissemination)

- A Venous  
B Arterial

tuberculosis supplemented by the presence of the acid-fast bacilli of tuberculosis in the depth of the lesion. Acceptable, however, is a lesion microscopically tuberculous granulation without bacilli demonstrable; the specific reaction being typical epitheloid and giant cell tubercles with extensive (lymphocytic) round cell infiltration, endarteritis and phlebitis in the surrounding tissues.

#### Chart II Experimental Gastric Tuberculosis

##### Operative Procedure

##### 1 Fundal Static Pouch



##### 2 Static Pyloric Pouch



##### 3 Static Achylic Cardiac Pouch



An ulcerative lesion is more common, representing over 80 per cent of the reported cases. Typically the pyloric lesions are multiple, occupy the lesser curvature, rarely exceed 2 cms. diameter, are usually shallow and rarely penetrates (incidents reported by Kundrat, Marfan, Paulicky and Struppler). Its irregularity with ragged over-hanging margins, edges, hyperemic edematous base covered with necrotic debris is usually greyish-yellow, simulate the enteric ulceration. It may eventually cause scarring and shrinkage



Fig. 1. Submucosal pyloric injection producing exudative response with acid fast organisms present.

of the stomach simulating syphilis or carcinoma. Instances of severe hemorrhage are extremely unusual.

The hypertrophic infiltration type is the second most common lesion producing a circumscribed tumefaction of submucosal origin causing extensive thickening and most frequently resulting in an annular constricting tumor.

Besides the above, in the apparent frequency of their occurrence, are encountered:

1. Characteristic caseous tubercles located in the submucosa occurring solitary or as a miliary involvement.

2. Multiple small erosions and ulcers of the mucosa as reported by Hamilton. These are superficial mucosal lesions with intense hyperemia and typical microscopy of tuberculosis.

### Chart III Gastroscopic Diagnosis In 50 Tuberculars

| Normal Mucosa | Atrophic Gastritis | Superficial (Acute or Chronic) | Ulcerative |
|---------------|--------------------|--------------------------------|------------|
| 19 (34%)      | 12 (24%)           | 11 (22%)                       | 8 (16%)    |

### Ulcerations Encountered

| Simple Benign Ulcer | Malignant Ulcer | Atypical Ulcer |
|---------------------|-----------------|----------------|
| 3                   | 1               | 4              |

3. A simple gastritis characterized by lymphocytic mucosal and submucosal infiltration.

4. "Cold Abscess" of the stomach.

5. Lymphangitic which is actually a tuberculosis perilymphangitis.

It may be suggested that gastritis preceded the caseous tubercles which in turn is brushed away to leave an erosion or ulceration which by conglomeration and extension forms the hypertrophic variety. Perhaps the types described are but stages of a progressive gastric tuberculosis. This hypothesis was suggested in our experimentation.

We herewith present a review of consecutive tuberculosis cases of Dibert and Breaux Memorial Tuberculosis Services of New Orleans, Charity Hospital in a span of 20 years ending in 1942. All patients were too far advanced for clinic management; all deaths were directly attributable to tuberculosis.

| Admissions | Deaths | Necropsies | Necropsy Enteric Tuberculosis | Necropsy Gastric Tuberculosis |
|------------|--------|------------|-------------------------------|-------------------------------|
| 23,276     | 7,146  | 1321       | 519 (25%)                     | 30 (0.22%)                    |

This study showed that all patients died with far advanced disseminated tuberculosis, that 25.4 per cent of cases showed enteric tuberculosis and that of these 5.8 per cent showed gastric tuberculosis which repre-

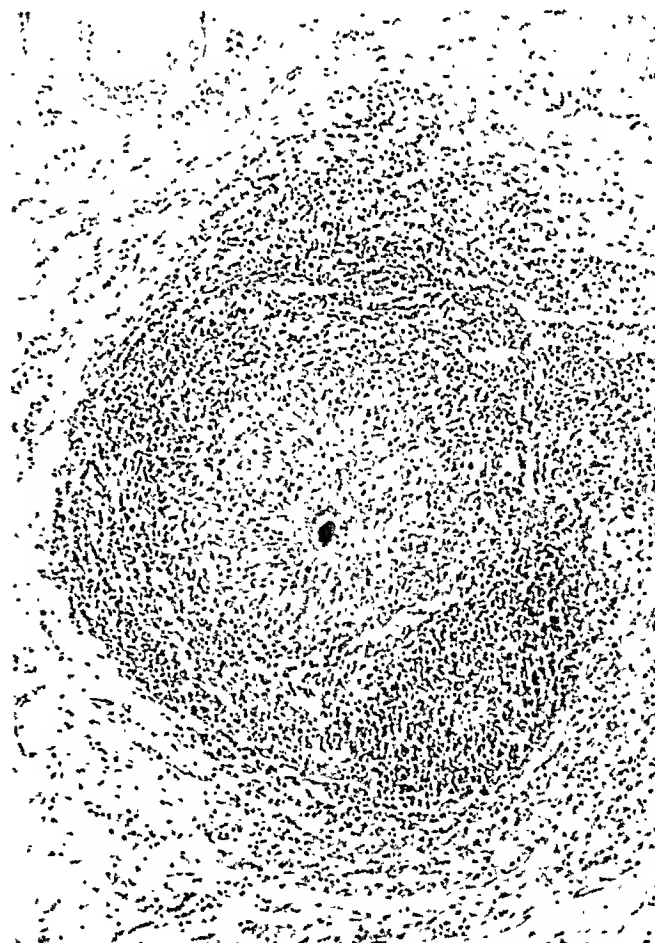


Fig. 2. Hematogenously produced epitheloid response in gastric submucosa.

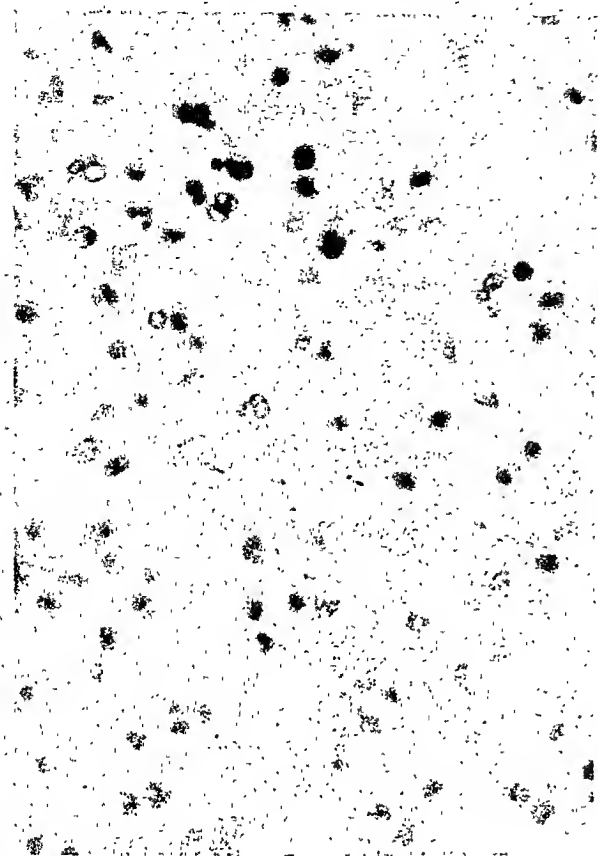


Fig. 3. Acid fast organisms demonstrated in lesion.

sented 0.22 per cent of the total necropsies and which broken down shows:

| Ulceration | Hypertrophic | Tubercles | Multiple Erosions |
|------------|--------------|-----------|-------------------|
| 17 (56.6%) | 10 (33.3%)   | 2 (6.6%)  | 1 (3.3%)          |

Unclassified gastritides were reported in 620 cases or 46.8 per cent, but we hesitate to draw conclusions for most of the autopsies were performed several days after the death of the patient when autolytic changes were far advanced. Rousseff, in a detailed study of 26 cases of pulmonary tuberculosis complicated by intestinal tuberculosis, found a definite gastritis in all cases. Hardt was able to demonstrate a gastritis in 14.2 per cent of 1000 autopsies of which 142 instances, 84 were chronic superficial, 40 were chronic atrophic and 18 were chronic hypertrophic gastritis.

In our series, 41 peptic ulcers (non-tuberculous) were encountered or 3.1 per cent approximating the 3.7 percentage reported by Portis and Joffe and the 4.4 per cent of Hardt and Cohen. Of these, 11 were gastric and 30 were duodenal.

Gastric carcinoma was present in 12 instances, no other neoplasm was encountered.

Gastric perforation as a result of tuberculosis ulcer, occurred in 3 instances.

## GASTROSCOPY

Schindler, in his text on Gastroscopy, gives adequate description of the tubercles, ulcerative and hypertrophic changes of tuberculosis of the stomach, but states "Theoretically it should be possible to see the typical gray nodules and to make the correct diagnosis, but the observer, as a rule, will not think of such a rare disease. If systematic observations of patients suffering from pulmonary tuberculosis were carried out, this might be different."

Besides those gastric lesions of tuberculosis which are too rare to explain the common dyspeptic tubercular, there must exist gastric mucosal changes which result from or are associated with the pulmonary process in some way. Olleres in a well conducted study of 23 gastroscopies on advanced cases of pulmonary tuberculosis, found an atrophic gastritis in three chronic superficial gastritis in eleven, and hypertrophic changes in seven. He assumes from his studies an allergic response of the gastric mucosa to produce a superficial gastritis, he considers the atrophic variety a result of malnutrition and not of acid fast origin.

In an effort to lend interest to the issue, we gastroscopied 50 Negroes in their third and fourth decades, with complicated bilateral pulmonary tuberculosis, who were febrile and severely toxic. The gastroscopic conclusion was agreed to in each instance by three of us studying each case.

Our findings revealed: (See Figs. 3 and 4).

## CONCLUSIONS

1. Our autopsy findings adhere closely to those of the literature.

2. Experimentally: (A) Acidity and stasis had no significance. (B) The fundal and cardiac pouches were not susceptible. (C) The pyloric pouch was susceptible to two methods of introduction. (D) The submucosal and hematogenous routes were the only successful methods of exciting a significant mucosal change.

3. Gastroscopically: (A) Normal mucosa represented 34.7 per cent. (B) Atrophic and superficial gastritis were of equal incidence. (C) Ulcers were more frequent than in routine gastroscopies. (D)



Fig. 4. Artist's concept of atypical prepyloric ulceration we considered probably tuberculous.



No gastritis of pathognomonic significance was established. (E) Of the lesions we classified atypical, two were suggestive of tuberculosis.

4. Our work leads us to expect that the continuation of this experimentation will permit us to produce and endoscopically observe development of mucosal

changes of tuberculosis and that thereby we may gastroscopically identify the same lesions in the human.

We should like to express our appreciation to Drs. T. Tilghman Herring and Reynold Pagzer who performed the surgical procedures.

## BIBLIOGRAPHY

- Ackermann, A. J.: *Am. J. Roent. and Radium Therapy*, 44:59-70, 1940.
- Adams, W. E. and Vorwald, A. J.: *J. Thoracic Surg.*, 3:633, 1934.
- Alexander, M.: *Arch. F. Klin. Med.*, 86:212-216, 1906.
- Baumgartner, W.: *Beitr. Z. Klin. Chir.*, 167:211-213, 1938.
- Biernath, P.: *Deutsche med. Wchnschr.*, 47:1091-1092, 1921.
- Broders, A. C.: *S. G. O.*, 23:490-498, 1917.
- Brown, Lawrason: *South. Med. J.*, 27:474, 1934.
- Cameron, O. J.: *Ann. Int. Med.*, 2:1265-1276, 1929.
- Clairmont, P.: *Bericht. Art. F. Klin. Chir.*, 76:180-322, 1905.
- Coats, J.: *Glasgow. Med. J.*, 26:53-61, 1886.
- Cohen, S. J.: *Nat. Tuberc. A. Tr.*, 28:184-186, 1932.
- Cohen, S. J.: *Am. Rev. of Tuberculosis*, 27:474, 1934.
- Curschmann, H.: *Beitr. Z. Klin. d. Tuberk.*, 2:127, 1904.
- Day, Alexander A.: *Quart. Bull. Northwestern U. Med. Sch.*, 15:39-45, 1941.
- Eichelberger, L. C. and McCluskey, K. L.: *Am. Rev. Tuberc.*, 17:533, 1926.
- Findel: *Ztschr. F. Hyg.*, 57:104, 1907.
- Good, R. W.: *Arch. Surg.*, 22:415-437, 1931.
- Gray, I. and Greenfield, I.: *Med. Clin. North America*, 20:551, 1936.
- Gray, I. and Ornstein, G. G.: *Trans. Am. Gastro-Enterological Ass'n.*, 35:229, 1932.
- Grayzel, D. M.: *Rev. of Gastro-Enterol.*, 2:204-207, 1937.
- Hamilton, A.: *Bull. Johns Hopkins Hosp.*, 8:75-79, 1897.
- Hardt, Leo L. and Cohen, S. J.: *Am. Rev. Tuberc.*, 43:628-636, 1941.
- Kine, M. and Rao, M. N.: *Brit. J. Surg.*, 25:379-386, 1938.
- Knollach, J. G. and Pape, R.: *Wien. Klin. Wchnschr.*, 47:1258-1290, 1934.
- Koch, Robt.: *The Etiology of Tuberculosis—English Translation New York National Tuberculosis Ass'n*, 1932.
- Leriche, R. and Mouriquand, E.: *Rev. de chir.*, 39:520, 1909.
- Melchior, E.: *Abstracted J. A. M. A.*, 87:888, 1926.
- Mills, M. A., Barth, E. D. and Gunn, F. D.: *Am. Rev. Tuberc.*, 42:28-57, 1940.
- Nedelec, M.: *Arch. Franco-Belger de chir.*, 34:76-104, 1934.
- Renander, A.: *Acta radio.*, 2:636-645, 1930.
- Rentschler, C. B. and Travis, R. C.: *J. A. M. A.*, 102:686-688, 1934.
- Ricard and Chevrier: *De la tuberculose et des stenoses tuberculeuses du pylore. Rev. de chir.*, Paris, 31:557-566, 1905.
- Rodriguez Ollerias, A. and de la Viera Garcis, P.: *Rev. espan. de enferm. d. ap. Digest y de la Nutricion*, 1:745-764, 1935.
- Schlesinger, H.: *Munch. Med. Wchnschr.*, 61:987, 1914.
- Simmonds, M.: *Munchen. Med. Wchnschr.*, 47:317-318, 1900.
- Sprunt, D. H.: *S. G. O.*, 51:245-248, 1930.
- Sullivan, R. C., Francona, N. T. and Dirshbaum, J. D.: *Ann. Surg.*, 112:225-233, 1940.
- Tappeiner: *Virchows Arch.*, 82:353, 1880.
- Van Wart, R. M.: *Bull. Johns Hopkins Hosp.*, 14:235-237, 1903.
- Walters, W., Kuklin, B. R. and Clagett, O. T.: *Proc. Staff Meet., Mayo Clinic*, 11:83-85, 1936.
- Watson, G. W., Flint, E. R. and Stewart, M. J.: *Brit. J. Surg.*, 24:333, 1937.
- Wessels, C. C.: *Am. Rev. Tuberc.*, 43:459-474, 1941.
- Woodruff, C. E. and Kelly, R. G.: *Am. Rev. Tuberc.*, 42:782-794, 1940.

## Histopathology of Chronic Gastritis\*

By

RUDOLF SCHINDLER, M.D.

and

MARIE ORTMAYER, M.D.

CHICAGO, ILLINOIS

IN 1808 Broussais described chronic gastritis as the most frequent, most important disease. Thirty years later his conclusions were shown to be based on post-mortem changes. This was never forgotten. The diagnosis "chronic gastritis" fell into disrepute. Even the careful histologic studies of Fenwick (2), Hayem (3), Rosenheim (8), Matthieu (6), Lubarsch (5) and Faber (1) did not overcome the prejudice. How could agonal changes be excluded? A new era appeared with the extensive use of surgical material gained at resections by Stoerk (12), Moszkowicz (7) and especially Konjetzny (4). Konjetzny found grossly visible acute erosive antrum gastritis in almost every ulcer bearing stomach. Contradictions arose from two sides; first the gastroscopist (9) stated he was unable to see the erosive gastritis described by Konjetzny; then Walters and Sebening (14) stated that those inflammatory changes were absent in the surgical material of the Mayo Clinic and assumed geographical differences. Later it was shown (10) that there were no geographical differences, that the acute erosive antrum gastritis of Konjetzny was an artefact caused by the act of resection (11). Interruption of the blood supply and presence of acid are able to cause an inflammatory reaction of the gastric wall with formation of erosions within two hours or less. Broussais' great

mistake had been repeated on a big scale, and only the observations of the gastroscopists prevented chronic gastritis from falling into oblivion again.

How could unobjectionable microscopic material of the gastric wall be obtained? Two ways were visible. The first one, that of gastroscopic biopsies, was chosen with great success by Swalm and Morrison (13). We thought that such biopsies did not yield sufficient material as to permit the development of a comprehensive histopathology of chronic gastritis. Therefore, we chose a second method, namely that of taking biopsies from the entire gastric wall at laparotomies, without the use of ligatures and clamps and with immediate fixation of that biopsy. The best place for taking the biopsy was determined by preceding gastroscopy. In rare cases additional fresh autopsy and resection material was used, namely in cases of certain histamine proved anacidity. We finally had at our disposal 52 sections of entirely reliable stomach material.

It is difficult to obtain normal material. However, Fig. 1 shows a section through the mucosa of an antrum which most likely is a normal one. The otherwise healthy man had an acute stricture of the esophagus. At laparotomy a biopsy without use of ligatures and clamps was taken. There seems to us to be a rather wide physiological range of infiltration of the interstitium and branching of the surface epithelium in the pyloric antrum so that it is not easy to de-

\*From the Frank Billings Medical Clinic, Department of Medicine, the University of Chicago, Chicago, Illinois.  
Read at the Annual Meeting of the American Gastro-Enterological Association at Atlantic City, N. J., June 8-9, 1942.





Fig. 1. Microscopic section of the normal human antrum. This section was gained at laparotomy by biopsy from the gastric wall without the use of ligatures and clamps in a man who had an esophageal obstruction but no stomach disease.

termine exactly where pathological changes begin. The section shows the regular surface epithelium, the rather deep pits, the branching pyloric glands and a medium amount of small cell infiltration between these glands.

In contrast to the antrum the normal histology of the body of the stomach is well established. The thickness of its mucosa varies depending upon its distention from 0.5 to 1.0 millimeters. The nodules seen so often in the post-mortem specimen, but not in the well distended stomach at gastroscopy have stalks which contain muscularis mucosae and submucosa. Fig. 2 demonstrates a section through a normal body mucosa. The epithelium of the surface and of the pits is a tall columnar epithelium, the oval nuclei lying regularly in one row in the lower third of each cell. The upper third contains mucus. The pits are shallow. Between them is a variable amount of connective tissue, containing lymphocytes, fixed fibroblasts, rare leukocytes and very scant plasma cells. There are only scant strands of muscle fibres and connective tissue between the long columnar glands, which as is well known, contain mucous neck cells, chief and parietal cells. The bottoms of the glands touch the muscularis mucosae, but at this point sometimes small accumu-

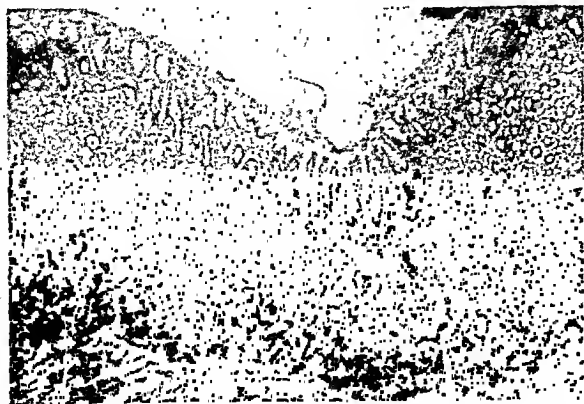


Fig. 2. Microscopic section through the normal human body mucosa of the stomach (biopsy from the gastric wall without use of ligatures and clamps).

lations of lymphocytes are seen which are not pathological.

When gastroscopically *superficial gastritis* was seen the microscopic picture obtained was different from the normal picture described in every case. The chief feature in all sections (Fig. 3) is the edema between the pits containing an increased amount of plasma cells, small hemorrhages and a fine net of fibrin. Small gaps in the surface epithelium on the top of hemorrhages are probably not artefacts. The presence of tremendous edema may become so severe as to cause flattening of the surface epithelium. In other cases real "catarrh" of the surface epithelium is seen. The cells are then stuffed with mucus, the nuclei being flattened out and even excavated by its pressure.

Transition from the superficial into an *atrophic* type of inflammation is frequent. The plasma cell infiltration becomes severe and due to its pressure at the neck of the glands retention cysts are formed. Proliferation of the pits start at this early stage. In



Fig. 3. Microscopic section of the gastric wall in chronic superficial gastritis. The section was gained by biopsy at laparotomy without the use of ligatures and clamps. Note that the edema between the pits contains an increased amount of plasma cells and hemorrhages. Some pits show flattening out of the nuclei of the epithelial cells due to the pressure of increased amount of mucus.

the epithelium of the cysts sometimes parietal cells are found, proving their origin from the glands. From below there is production of connective tissue which in triangular cushions rest on the split up muscularis mucosae. Proliferating infiltration destroys the glands, and sometimes isolated parietal cells are found within this granulation tissue. Large irregular lymph follicles are formed, the glands now being gone almost entirely (this has been called follicular gastritis). The pits start to proliferate and to grow toward the muscularis mucosae. Edema may become still more outspoken. The proliferating pits look tortuous and branching. During this proliferation the epithelium of the surface and of the pits undergo sometimes a metaplastic change into an intestinal type. The regular mucus forming cells are replaced by serous cells, but between them there appear many goblet cells, so that the total amount of mucus seems to be increased as compared with the normal mucosa. So-called Russell bodies, iron carrying derivatives from plasma cells are found in the interstitium. Sometimes proliferation of the surface epithelium will develop. This has been



Fig. 4. Section through the gastric body mucosa in a case of chronic atrophic-hyperplastic gastritis. Almost all glands have disappeared. The remnants of the glands have lost their specific character. In the left lower field ectopic glands within the muscularis mucosae are seen. There is much interstitial infiltration and one enlarged unsharply limited lymph follicle. The surface epithelium is proliferating and forming irregular nodes. Some goblet cells are seen.

called "atrophic-hyperplastic gastritis" (Fig. 4). Real nodules may develop and rarely even ulcerations and formation of pseudopolyps will be found. The mucosa shrinks more and more. Finally, all glands are gone and the surface epithelium is resting immediately on the muscularis mucosae. This then is an atrophy due to an inflammatory process.

If we define *hypertrophic gastritis* as inflammation of the entire gastric mucosa more severe than a mere catarrh, but without reduction of the amount of glands, then we have to state first that it was impossible to find transition from such pictures to atrophic gastritis. We may differentiate microscopically three different forms.

1. The first form may be called *interstitial hypertrophic gastritis*. Extensive small cell interstitial infiltration and a reaction of the lymphatic tissue is



Fig. 5. Microscopic section through the body mucosa of the stomach in a case of chronic proliferative hypertrophic gastritis. The glandular portion of the mucosa is of normal structure and thickness but on the top of it there is grotesque irregular proliferation of the surface epithelium with infiltration. There is formation of large nodes (biopsy from the gastric wall without use of ligatures and clamps).

seen, but only little proliferation of the surface epithelium.

2. The second form may be called "proliferative hypertrophic gastritis"; (Fig. 5) the glandular portion of the mucosa is of normal structure and thickness, but on the top of this glandular layer there is a grotesque irregular proliferation of the surface epithelium forming large nodes. The epithelial cells are decidedly pathological. They lose their capacity of forming mucus; the nuclei are lying in several irregular rows. True cell syncytia are formed. These are the cases in which the pathologist may find trouble in differentiating between tumor and gastritis.

3. The third form could be called *glandular hypertrophic gastritis* (Fig. 6); at the first glance one could think that he is dealing with a rather normal mucosa, but measuring of the thickness of the mucosa shows that its diameter is tripled and that the large nodes visible are due to an overgrowth of the glandular apparatus. In contrast to the nodes of the normal mucosa these have no stalks. One could think that this is a noninflammatory growth of the mucosa, but frequently definite signs of inflammation, such as edema,

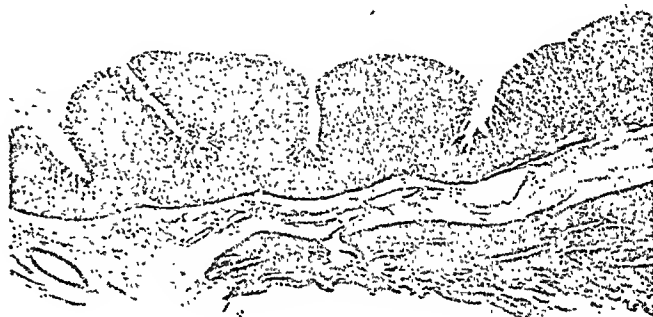


Fig. 6. Microscopic section through the body mucosa of the stomach in a case of chronic glandular hypertrophic gastritis. The thickness of the mucosa is tripled. Large irregular nodes are formed by the proliferating glandular apparatus. Some cysts are seen (biopsy from the gastric wall without use of ligatures and clamps).

formation of cysts filled with leucocytes and plasma cell infiltration are found together with the glandular proliferation.

Only typical pictures have been chosen, and rare unusual cases have been omitted. However, the histopathology of chronic gastritis seems now to be well established.

## SUMMARY

Taking of biopsies from the gastric wall at operation without the use of ligatures and clamps was used in order to get unobjectionable material for the study of the histopathology of chronic gastritis. In addition, some sections gained at operation or at autopsy were used in cases in which the histamine test had shown a complete anacidity. The typical pictures of the normal gastric mucosa, of superficial gastritis and of the various forms of atrophic and hypertrophic gastritis have been described.

## REFERENCES

1. Faber, K.: *Gastritis and Its Consequences*. Milford, Oxford University Press, London, 1935.
2. Fenwick, W.: *On Atrophy of the Stomach and on Nervous Affections of the Digestive Organs*. London, 1880.

3. Hayem, G.: Des gastrites dégénératives. *Bull. Soc. méd. Hop.*, Paris, 1896.
4. Konietzky, G.: *D. Entzündung d. Magens in Henke, F. u. Lubarsch, O. Handb. d. spez. pathol. Anat. u. Histol.*, Berlin: Springer, 1928-4, Bd. 2 Teil p. 768-1126.
5. Lubarsch, O.: *Pathol. Anat. u. Histol. d. entz. Erkrank. d. Magens, 6 Tagung Ges. Verdauungskr.*, Berlin, 1926.
6. Matthieu, A.: Etat de la muqueuse de l'estomac dans le cancer de cet organe. *Arch. Gén. de Méd.*, 163:402, 1889.
7. Moszkowicz, L.: *Z. Histol. d. ulkusbereiten Magens Arch. Klin. Chir.*, 122:444, 1922.
8. Rosenheim, Th.: Über atrophische Prozesse an d. Magenschleimhaut in ihrer Beziehung zum Carcinom, etc. *Berl. klin. Wochenschr.*, 25:1021, 1888.
9. Schindler, R.: Ulkus u. Gastritis. *Verh. d. Gesellsch. f. Verdauungskrankh. 6 Tagung*, Berlin, Oct., 1925.
10. Schindler, R.: The Incidence of Various Types of Gastric Disease as Revealed by Gastrosopic Study. *Am. J. Med. Sci.*, 197:509, 1939.
11. Schindler, R., Necheles, H. and Gold, R.: Surgical Gastritis: A Study on the Genesis of Gastritis Found in Resected Stomachs, etc. *S. G. O.*, 69:281, 1939.
12. Stoerk, G.: Über Gastritis chronica. *Wien. klin. Wo.*, 44:855, 1922.
13. Swalm, Wm. A. and Morrison, L. M.: Gastrosopic and Histologic Studies of the Stomach with Gastric and Extra-Gastric Disease During Life and at Autopsy. *Am. J. Dig. Dis.*, 8:391, 1941.
14. Walters, W. and Sebenius, W.: A Comparison of Lesions Associated with Duodenal Ulcer in Germany and in the U. S. *Minn. Med.*, 15:579, 1932.

## DISCUSSION

DR. LEON SCHIFF (Cincinnati, Ohio): Mr. President and Members and Guests: I think that the papers of both Dr. Schindler and Dr. Renshaw are particularly timely and important. I think there is a great need for further histologic studies not only in gastritis but also in normals.

I just want to say a word about accidents resulting from the use of the flexible gastroscope. We have had three gastric perforations in thirteen hundred examinations, one presumptive and two proved. In the proved cases the perforation occurred at the time the instrument was introduced and produced no immediate pain. The perforations were high on the posterior wall, the usual location, according to Schindler, of this type of traumatic perforation.

One patient was operated on about thirteen and one-half hours after the gastrosopic examination and recovered after a stormy course. The second case was operated three hours after the accident but died seventy-two hours later. This, I believe, marks the first reported fatality from gastric perforation following use of a flexible gastroscope.

In discussing the matter with Dr. Mont. Reid of our Surgical Department, we felt that since the perforation is rather hard to approach because of its location, and since the stomach is empty at the time of examination, it might be wise not to operate immediately. In the first case in whom no operation was performed, recovery was uneventful.

Since gastroscopy may result in such a serious accident, we believe that this in itself offers a strong argument against carrying out the examination unless there is a distinct indication for it. I am sure that the procedure is here to stay and I know it has advanced and will continue to advance our knowledge of gastric disease; nevertheless, it must be remembered that like any other endoscopic procedure, it has its limitations and its risks.

DR. HENRY A. RAFSKY (New York): My contribution to this discussion is to show some intragastric photographic studies, in natural colors, which were made in conjunction with gastroscopy. The method which was employed was as follows: The gastroscope was introduced. Then the depth of the instrument was measured and this distance was outlined on the flexible tube to which the camera was attached. After the photographs were taken they were sent to Eastman Kodak where they were developed. Then they were enlarged. Slide 1 shows a normal mucous membrane. Slide 2 is that of a prepyloric ulcer. Only the edge of it was caught by the camera but we do see an area of hypertrophic gastritis contiguous to the ulcer presenting a typical cobblestone appearance. Enlarged folds in the rest of the stomach can also be seen.

Slide 3 demonstrates a prepyloric ulcer which was treated by duodenal alimentation. Three weeks later I again looked for the ulcer, but I could hardly see a trace of it. There was not enough present for another photograph. This case shows definitely that gastric ulcers do heal with medical treatment. Slide 4. In this case the edge of a bleeding ulcer was caught by the camera but the important part of this colored photograph is that the enlarged folds which we see do not present the typical appearance of hypertrophic gastritis or atrophic gastritis, but as Dr. Schindler mentioned before a variety of hyperplasia. I felt it was a hyperplastic gastritis, which we see in various affections. This phase of the subject cannot be gone into at the present time but I do think it is misleading to term these areas "hypertrophic gastritis." Slide 5 shows a carcinoma dipping into the pyloric outlet. This is exactly the way the lesion looked through the gastroscope and also how it appeared when the resected specimen was examined. Slide 6. This is another case of a carcinoma in the prepyloric area; along side of it is another view which I did not see through the gastroscope. The camera caught the little nodules which can readily be seen. Slide 7. This case is rather interesting. The carcinoma was readily seen in the prepyloric region. It was springing from one point. The folds contiguous to it were flattened but the rest of the mucous membrane appeared to be normal. This was the gastrosopic view and the resected specimen was similarly described by the pathologist. This case brings up the question whether the atrophic gastritis preceded or followed the malignant lesion. From this photograph I am inclined to think the latter occurred. Slide 8 presents a very interesting photographic view of a gastrosopic finding. From this slide you would think that you were looking at the pylorus, that was the gastrosopic impression. But what this view actually represented was the one end of an opening of a cicatrized canal in which there was a small carcinoma starting one-half a millimeter from the pyloric end and which was 2½ millimeters wide. The pyloric outlet was beyond the field of visualization. These slides demonstrate the fact that at times we see something through the gastroscope and the camera may also catch it but the pathological specimen does not verify our findings.

DR. JULIAN M. RUFFIN (Durham, N. C.): Mr. President and Gentlemen: In recent years a wave of enthusiasm for gastroscopy has swept over the country, so much so that the procedure is practiced in practically every part of the United States. At this stage it seems to be wise for the profession to pause and review critically the procedure, weighing its value against its limitations.

Dr. Renshaw has given us just such a critical review and is indeed to be congratulated upon the conservatism of his paper. The more gastroscopies I do, the more I am convinced of this fact: What one sees, one sees clearly and unmistakably, but how much one doesn't see is a matter of conjecture, and in Dr. Renshaw's paper he stated that in 9 per cent of his cases the procedure was unsatisfactory, because a certain portion of the stomach was not seen, and in 50 per cent there was a large, blind area. My findings are entirely in agreement with those of Dr. Renshaw throughout the whole of his discussion.

Dr. Hardt's paper is interesting indeed. It is not surprising that one should find atrophy of the gastric mucosa in patients having pulmonary tuberculosis. However, it is probably a local manifestation of a general condition, not gastritis at all, but a degenerative process, due to inadequate nutrition or to an actual vitamin deficiency.

Dr. Browne's paper was extremely interesting. I have had no practical experience with this, but will comment on it only to say it is a very valuable contribution.

Dr. Schindler's work speaks for itself. The slides which he showed cannot be questioned. However, I wish to take this opportunity to express my views on the general

subject of gastritis. Granting that chronic gastritis is widespread throughout certain sections of the country, still our experience leads us to believe that it is not common in North Carolina. Superficial and hypertrophic gastritis are rarely seen. Atrophy of the gastric mucosa, however, is common and occurred in 14 per cent of 1,000 cases. This is rather to be expected since deficiency states are frequently seen in the clinics of Duke Hospital. However, it would be wiser to use the term "atrophy of the gastric mucosa" rather than "atrophic gastritis," since it is probable that this represents a degenerative rather than an inflammatory process.

Finally, it should be emphasized that chronic gastritis is not as widespread as it is thought to be, that it gives rise to no recognizable clinical picture, and that the whole subject should be given more critical thought.

DR. IRVING GRAY (Brooklyn, N. Y.): Mr. President, Ladies and Gentlemen: At the Seaview Hospital in Staten Island, there are approximately 1800 patients constantly under care for chronic pulmonary tuberculosis. I have reviewed the autopsy statistics on the question of gastric changes in advanced pulmonary tuberculosis and wish to make several comments in reference to Dr. Browne's presentation.

In our studies of 2000 autopsies the incidence of tuberculous ulcer of the stomach was 0.54 per cent. In every instance of tuberculosis of the stomach intestinal tuberculosis was present. Patients with pulmonary tuberculosis frequently swallow their sputum. Criteria for the diagnosis of these tuberculous gastric ulcers have been well discussed by Dr. Browne. In our studies the ulcer in all instances was located in the pyloric region of the stomach. The ulcer usually had a dirty gray to dirty yellow base and was covered by irregular overhanging edges.

The presence or absence of gastritis in these patients who came to autopsy could not be clearly evaluated. Many of these patients did not come to autopsy until six to twelve hours after death. The changes present in the gastric mucous membrane may have been due to post-mortem factors. In evaluating the entire question of gastritis in patients with chronic pulmonary tuberculosis it would seem advisable that if gastroscopic findings are to be used as the basis for diagnosis of gastritis that the findings be evaluated according to age groups in conjunction with the duration of the underlying pulmonary tuberculosis.

DR. RUSSELL S. BOLES (Philadelphia): I should like to ask Dr. Browne one question. I noticed on one of his slides that there were 1321 necropsies, with a 25 per cent incidence of enteric involvement. I should like to ask what he means by "enteric involvement"; does he mean ulcerative disease or serosal disease, or both? If it means ulcerative disease, it is the lowest figure that I have any knowledge of in individuals dying of tuberculosis.

It has been my experience, having been much interested in this subject, to observe close to 75 per cent involvement of an ulcerative type in the intestinal tract in individuals dying of tuberculosis; and I think most of the literature reports as high as even 80 or 90 per cent in individuals dying of tuberculosis. If that is the case, his figures do not adhere closely to those in the literature, as he states, if I am correct in interpreting his slides.

DR. R. JOHN F. RENSCHAW (Cleveland): Mr. President, in the first place I should like to express my gratitude to the Program Committee for accepting our humble efforts. I realize that I am talking to a group of experts who probably have forgotten more gastro-enterology than

I know, but this first presentation is a part of our efforts to re-evaluate gastroscopy. We were emphasizing some of the technical difficulties in the hope that the clinicians and our confrères would bear in mind that while gastroscopy might be of major help, it will fail in approximately one-fifth of the cases.

The work that Dr. Ruffin and Dr. Schindler have done further emphasizes the efforts to re-evaluate the procedure, and we shall need more studies of that nature. I think they are to be congratulated.

I wish to make one point about the term "chronic gastritis." It is my opinion that some of the misunderstanding about the clinical significance of chronic gastritis has come from the fact that we use the word "gastritis" rather than "gastric change," or "hypertrophy," or "atrophy." I think if we would use the term "hyperplasia" or "atrophy," and let the clinician decide whether it is active gastritis and of clinical importance, we would have lower incidence of so-called gastritis causing symptoms.

In my own experience gastric mucosal changes apparently responsible for symptoms do not exceed 15 per cent, and I believe more accurately it is about 6 per cent.

Dr. Rafsky's last slide is extremely important. It emphasizes the point that the gastroscopist cannot always be sure that he has seen the area in question.

DR. LEO L. HARTDT (Chicago): I feel very much as Dr. Ruffin has expressed, and as Dr. Renshaw has also mentioned—we frequently neglect to consider the patient as a whole when we peek through the gastroscope. If we did, we probably would find a larger group of these cases classified as atrophic changes rather than atrophic gastritis.

Our group was in patients who for the most part lost considerable weight and were suffering from a degenerative, wasting disease. In this group we frequently have seen cases similar to what Dr. Ruffin has described in patients suffering from Vitamin B deficiency.

I wish to thank you, Mr. President, and the members of the Association for having had the opportunity of presenting this paper.

DR. DONOVAN C. BROWNE (New Orleans): Dr. Gray's statistics I find are essentially in accord with what we have found, with one or two exceptions.

Dr. Rafsky's photography stressed one thing I have thought of, that until the gastroscope is improved to the point where actual photographs may be taken through it, when you have once localized a lesion, we have the individual element to contend with in any report that comes out on gastritis.

Dr. Boles' question concerns the ulcerative and enteric group. The group that we had designated "enteric" is tuberculosis, that involved the gastro-intestinal tract and, if I remember correctly, there were 78 per cent of those. There are many things you can't put in ten minutes, but 78 per cent of them have ulcerative type in other parts of the bowel, and so forth. I wouldn't be sure of that, but I have the breakdown complete, which I would be very pleased to give you later.

DR. RUDOLF SCHINDLER (Chicago) (closing the discussion): To Dr. Schiff's discussion I want to say we have been lucky enough not to have one single accident in the last over 3900 gastroscopies. I think Dr. Ruffin's presentation would be still more convincing if he would be able to present the microscopic evidence that what he calls normal mucosa really is normal mucosa. I agree with almost everything Dr. Renshaw said. I think it was most important. I want to congratulate Dr. Rafsky; his colored photographs are wonderful.

## The Secretion of Water as a Component of Gastric Acid Secretion\*

By

HORACE W. DAVENPORT, Ph.D.  
PHILADELPHIA, PENNSYLVANIA

THERE are two fundamentally opposed theories of the mechanism of gastric acid secretion. The first (1, 2, 3), for convenience called the "parietal cell theory" is that the parietal cells secrete hydrogen ions at the concentration at which they ultimately appear in the gastric juice, 0.159 N. The principle of electrical neutrality of solutions requires that chloride ions move from the blood through the parietal cells in order to accompany the hydrogen ions. Throughout the process of secretion there is no change in the concentration of water, and no work is done on it by the secreting cells. The acid secretion while it is being formed and secreted is always isotonic with the blood. The fact that gastric secretions as they are collected in pouches or through fistulas are sometimes hypotonic is attributed to the loss of carbon dioxide from the solution (2).

An opposing theory has been suggested in various forms by several authors (4, 5, 6). This theory which might be called the "cycle theory" supposes that the parietal cells secrete dilute hydrochloric acid whose hydrogen ion concentration is about  $10^{-5}$  N. As this solution passes through the tubules of the gastric glands water is absorbed from the dilute solution by the cells lining the tubules. When the solution issues from the mouth of the gastric glands so much water has been reabsorbed that the solution is isotonic with the blood, and the hydrogen ion concentration is raised to 0.159 N.

It is the purpose of this paper to discuss these two opposing theories in relation to the roles they assign to water in the secretion. It will be shown that the first theory, though not proved, is plausible while the second theory is untenable.

It is well established (2, 4) that the acid secretion as it appears in the stomach is isotonic with the blood. This means that the gastric glands need do no osmotic work on the water in the course of forming the secretion, for no energy is gained or lost when water moves from one solution to another which is in osmotic equilibrium with it. On the other hand if the parietal cells secrete a dilute hydrochloric acid solution from which water is later reabsorbed they must perform osmotic work on the water. Water exists in the blood at a mol fraction of 0.994 (7), and it would exist in the postulated dilute solution at a mol fraction of 1.00. In raising the concentration of water from the lower to the higher mol fraction the cells would have to do work just the same as though they raised the concentration of a solute. This postulated work is undone as the water is reabsorbed in the tubules. Thus water is supposed to go through a cycle of secretion and reabsorption which is unnecessary. The principle of logic that hypotheses must not be needlessly multi-

plied requires that the cycle of water secretion and reabsorption should be rejected until it is proved necessary.

If the parietal cells secrete a dilute acid solution containing hydrogen ions at a concentration of about  $10^{-5}$  N it would be required that the glands secrete 16,000 liters of this dilute solution in order to make one liter of acid gastric juice. This would require that for every liter of acid juice appearing at the mouth of the glands 16,000 liters were secreted by the parietal cells and 15,999 liters of water were reabsorbed. The kidneys, organs specifically fitted to perform this sort of work, ordinarily reabsorb about 100 liters of water for every liter of urine secreted, and there is no evidence that the gastric tubules are 160 times more active than the kidneys in reabsorbing water.

Although the change in the concentration of water required by the "cycle" theory is small the enormous volume required to be secreted for every liter of acid juice finally formed makes the energy cost prohibitive. It can easily be calculated that if 16,000 liters of water are secreted for every liter of acid juice appearing in the stomach 59 large calories would be expended. The "parietal cell theory" requires only 1.5 large calories. If 59 large calories were expended for every liter secreted the increase in energy consumption attending increased gastric secretion would be easily detectable. However no increase in the energy consumption of the body attributable to the work of the gastric glands has ever been found, and it can be concluded that the large energy cost of the "cycle theory" is more than is actually expended in the formation of the acid secretion.

A final argument can be drawn from the gastric secretion of acetylsulfanilamide. The same argument could be made for many other substances, but acetylsulfanilamide is chosen because the ratio of its activity coefficients in plasma and gastric juice is nearly unity (8). It has been shown that acetylsulfanilamide diffuses rather slowly through the tissues of the body. This means that when the parietal cells are forming a secretion at a finite rate the concentration of acetylsulfanilamide in their secretion would be about 30% of that in the plasma. Now if large quantities of water were reabsorbed from the parietal cell secretion in the tubules of the gastric glands, the concentration of acetylsulfanilamide in the solution remaining in the tubules would rise greatly in the same way the concentration of some solutes rises in the tubules of the kidney. On account of the slowness of the diffusion of acetylsulfanilamide through the tubule cells only a fraction of the acetylsulfanilamide in the tubules would be reabsorbed with the water. Even if very much less than 99% of the water in the tubules were reabsorbed the concentration of acetylsulfanilamide would rise past the saturating concentration; the drug would crystallize; and the gastric juice would be satu-

\*From the Department of Physiology, Medical School, University of Pennsylvania.

Read at the Annual Meeting of the American Gastro-Enterological Association, Atlantic City, N. J., June 8-9, 1942.



rated with acetylsulfanilamide. This does not happen, for the concentration of acetylsulfanilamide in the gastric juice is only about a third of that in blood (9). On the other hand in the kidneys where such filtration and reabsorption does occur, acetylsulfanilamide does reach the saturating concentration, and crystalline casts of the drug are often found in the urine. Consequently such a cycle cannot occur in the gastric mucosa.

These lines of argument lead to the conclusion that the "cycle theory" is untenable. Since the central concept of the "cycle theory" is that the parietal cells secrete a dilute solution of hydrochloric acid that concept must be abandoned. Any attempt to save the theory by the addition of other postulates results in even greater difficulties than have been exposed in this paper. Therefore the conclusion that the parietal cells actually secrete isotonic hydrochloric acid should be accepted until overwhelming experimental evidence to the contrary is obtained.

### REFERENCES

1. Davenport, H. W. and Fisher, R. B.: The Mechanism of the Secretion of Acid by the Gastric Mucosa. *Am. J. Physiol.*, 131:165-75, 1940.
2. Gray, J. S. and Bucher, G. R.: The Composition of Gastric Juice as a Function of the Rate of Secretion. *Am. J. Physiol.*, 133:542-50, 1941.
3. Gray, J. S.: The Formation of Acid by the Gastric Glands. Symposium on the Mechanism of Secretion. Boston Meetings. American Physiological Society, 1942.
4. Gilman, A. and Cowgill, G. R.: The Regulatory Action of Total Blood Electrolytes on the Concentration of Gastric Chlorides. *Am. J. Physiol.*, 99:172-78, 1931.
5. Dawson, A. B. and Ivy, A. C.: Formation of Hydrochloric Acid by the Gastric Mucosa. *Am. J. Physiol.*, 76:158-69, 1926.
6. Hoerr, N. L. and Bensley, R. R.: The Mechanism of Secretion of Hydrochloric Acid in the Gastric Mucosa. *Anat. Record*, 65:417-35, 1936.
7. Borsook, H. and Winegraden, H. M.: The Work of the Kidney in the Production of Urine. *Proc. Soc. Nat. Acad. Sci.*, Washington, 17:3-12, 13-38, 1931.
8. Davenport, H. W.: The Mechanism of the Secretion of Sulfonamide Drugs in Gastric Juice. *Yale J. Biol. and Med.*, In press.
9. Cooke, M., Davenport, H. W. and Goodman, L. S.: The Secretion of Sulfonamide Drugs in Gastric Juice. *Yale J. Biol. and Med.*, 14:13-28, 1941.

### DISCUSSION

DR. FRANKLIN HOLLANDER (New York): I hadn't planned to discuss Dr. Davenport's very interesting paper,

because I was in hopes that Dr. Visscher would be able to present his evidence, but since he is not, may I point out one very interesting phenomenon which I reported on some years ago in the course of investigation of this problem, and which Dr. Visscher and his associates have amplified more recently, which I think he was going to report on today.

It is this: that when we collect what is nearly pure parietal secretion from gastric pouches, juice which has around 160 clinical units, and chloride of practically no neutral chloride, and when we make freezing point and pressure tests on it, we find that the liquid is not isotonic with circulation but a little bit hypertonic, and the discrepancy, so far as our calculation is concerned, is not greater than 5 per cent, and most of the time a little bit less.

This is an interesting phenomenon for us all, though the difference is quite slight. It is interesting because it suggests there are probably other forces at work in the parietal cell or in regard to the relation of the parietal cell to the surrounding tissue fluids, other forces which make for a concentration force of some kind, so the parietal secretion as it is formed is a little more than isotonic in concentration.

I would be interested if Dr. Davenport would give us his ideas on this finding.

DR. HORACE W. DAVENPORT (Philadelphia) (closing the discussion): I am sorry I can't discuss the technical matter of the osmotic determinations very well and I am sorry I couldn't hear Dr. Visscher's paper. I believe he found somewhat hypotonic solutions, but it is only hearsay. I want to caution people as to the extreme difficulty of determining osmotic pressures, and the freezing point method seems to be somewhat unreliable. I think that even the best Hill method sometimes goes bad, and I must merely leave the question open, with a large question mark attached to it.

I am sorry that we can't have positive evidence on this score to answer the theory, but perhaps it may be the parietal cells are so extremely inaccessible that we can do no more than speculate occasionally.

## Parotid Duct Obstruction Without Calculus\*

### A Suggestion for Treatment

By

LOUIS PELNER, M.D.

BROOKLYN, NEW YORK

ONE of the most obvious and easily discernible effects of a powerful parasympathetic stimulant is marked salivation. One wonders why advantage has not been taken of this fact in therapy, e.g., in salivary duct obstructions. One reason is probably the supposed rarity of salivary duct blockage. While salivary duct stone is relatively uncommon, the same apparently does not hold for salivary duct obstruction without stone. The rarity of salivary duct calculus is shown by the figures quoted from the Russian clinic (1), as one case in about 14,000 patients. In some countries, perhaps because of dietary habits the incidence is greater. The prevalence of salivary duct obstruction

without stone is attested to by the fact that four cases were seen during a very short interval in a general clinic and medical practice.

C. P. Howard (2) listed under the term Sialodochitis Fibrinosa, a condition similar to the cases to be described, i.e., parotid duct obstruction without calculus. Kussmaul (2) in 1879 suggested that purulent or fibrinous plugs can obstruct the salivary ducts and cause symptoms suggestive of stone. Emden (2) in 1897, and Greig in 1911 each gave an excellent description of the clinical picture: A recurrent swelling of the parotid gland that lasted for many days, becoming extremely large following the ingestion of food, and terminating with the expulsion from the duct of plugs of fibrin and a profuse flow of saliva.

\*From the Department of Medicine, Jewish Hospital of Brooklyn, Dr. J. Rosenthal's Service.  
Submitted July 15, 1942.



Emden considered the possibility of secretory neurosis as the basis for this condition. Recently an English investigator (3) stated that this condition, which he called a recurrent subacute parotitis without the presence of salivary calculi, was invariably due to a mild degree of infection of the parotid ducts. The secretions in these cases were exceptionally mucoid in type, and at times plugs of mucus and casts of the main duct were obtained by parotid massage and catheterization. He pointed out that the parotid being a serous gland, has a thin watery secretion almost free from mucus, but traces could be derived from the larger ducts. When the duct is inflamed, the mucoid secretion is markedly increased, and along with pus cells and epithelial cells forms plugs which obstruct the duct, and dam back the normal serous secretion. It is possible that this condition is occasionally a precursor of parotid calculus. It is conceivable that with a viscid secretion of this type, if the stasis in the duct was prolonged for a sufficient length of time, we might eventually get a precipitation of the secretions. Undoubtedly, the medium of the mouth would be all important in this connection.

### ANATOMY AND PHYSIOLOGY

It might be worth while in order to understand the method of treatment indicated, to review briefly the anatomy and physiology of the parotid gland. This gland (4) is situated in front of the ear and folded around the ramus of the mandible. The duct of the parotid (Stenson's duct) empties into the mouth opposite the second molar tooth. The gland itself is histologically divided into lobes and lobules. The duct is divided into a larger excretory part and a smaller secretory part: the latter is made up of columnar cells exhibiting secretory granules. The secretory duct is in turn divided into smaller ducts which connect with lobes, lobules and finally alveoli. In general, there are two types of salivary cells—serous and mucous. The alveoli of the parotid gland are composed of only one type, serous which secrete thin watery fluid. The protoplasm of either the serous or mucous cells is not homogeneous, but shows a granular structure due to the presence of minute colloidal droplets. The granular appearance is different in the two cell types. In the serous cell, they are fine and are so numerous as to fill the cell in the resting state of the gland. These granules are termed zymogen granules because they are thought to furnish the enzyme of the secretion. After prolonged secretion the granules are discharged along with the other constituents of the juice. After a period of rest, they gradually re-accumulate in the cell.

Two types of nerves enter the parotid gland (5), the parasympathetic fibres which are the true secretory nerves, and the sympathetic fibres. Stimulation of the parasympathetic fibres of the parotid causes an abundant watery secretion, but no secretion occurs following stimulation of the sympathetics. However, a reduction of zymogen granules has been observed to occur, so it must be assumed that sympathetic stimulation has some effect. In other salivary glands stimulation of the sympathetic nerve causes a thick mucoid type of secretion. That the secretory part of the parotid duct may also take part in secretion, especially at certain times, can be seen from the character of its cells.

The thick mucoid material observed in the cases

herein cited, might be due to an infection of the parotid secretion, but may also be due to an over-preponderant sympathetic stimulus to the parotid duct.

### SYMPTOMATOLOGY AND DIFFERENTIAL DIAGNOSIS

The symptomatology of this condition is essentially similar to the description given by Emden (2). There is a recurrent swelling of the parotid gland, accompanied by pain, just before or during mealtime. There is a discharge of a thick mucoid secretion into the mouth, often having a disagreeable taste. The patient may complain of pain in the ear or along the side of the cheek. X-ray examination as well as bimanual examination would reveal no calculus.

Obstruction (6) of the parotid duct must be differentiated from all other glandular swellings due to cysts and lues, acute inflammatory lesions such as epidemic parotitis and post-operative parotitis, actinomycosis, lymphadenitis from infected tonsils and teeth, Mickulicz's disease and malignancy of the parotid. Obstruction of the parotid duct whether due to stone or inspissated secretion can usually be differentiated by the history of intermittent swelling of the gland and pain just before or during meals. Bimanual examination would reveal a calculus if it were present. X-ray examination is positive in from seventy to eighty-five per cent of these cases of calculus. The history would serve to rule out epidemic parotitis, post-operative parotitis and actinomycosis. Malignancy of a parotid would be the most difficult condition to rule out, but the history of remissions and the results of the simple therapy to be described would serve to differentiate it.

### CASE REPORTS

Cases 1 and 2. Two of the cases of parotid duct obstruction without calculus were essentially similar and can be discussed together. One was in a male, (J. P.) age 30, and another in a female, (M. G.) age 46. The first patient had had several recurrent attacks, while the second was seen in her first attack. The symptoms were the same in both. Marked swelling of the parotid gland was present usually with the exacerbation before and during every meal. A thick mucoid secretion was seen coming from a pouting Stenson's duct. There was difficulty in opening the mouth in both patients. Calculi could not be palpated and radiography proved negative in both. The duration of the attack was four weeks in the first patient and two weeks in the second. Catheterization of Stenson's duct proved of limited benefit to either patient.

Prostigmine methylsulphate 1/2000, 1 cc. was given to each patient hypodermically. In each case, in about 25-30 minutes a profuse watery excretion occurred, lasting for many minutes. Following this, the gland receded in size and the enlargement had not recurred for about four months in the first instance and for about six months in the second.

Case 3. I. C., 56 year-old female patient first came to the clinic in 1931, when she complained of swelling of the right cheek and face of four days duration. The swelling was present two weeks before and then subsided. Examination at the time of first admission showed a marked swelling of the right side of the face. Stenson's duct on that side exuded a thick pus. An X-ray apparently was not taken. Two days later the patient stated that she passed a calculus with a profuse evacuation of pus. An X-ray taken after this event showed no calculus. However, the swelling in the face persisted and had to be incised externally. The "pus" proved to be sterile. The

patient is a mild diabetic, and has among other findings, an apparently innocuous calcific plaque in the cerebellar region of the brain. She was seen in the clinic recently, because of dryness of the right side of the mouth and small ulcerations beneath her dental plate which resisted all treatment. Investigation showed that no saliva was exuding from the right Stenson's duct. A large swelling was present in the parotid region. One cc. of prostigmine methylsulphate 1/2000 was given hypodermically. In twenty minutes a profuse salivation occurred. The gland was slightly tender. The patient was told to apply a hot water bottle while at home. The secretion continued, although at a diminished rate, until she was seen two days later. At that time another dose of prostigmine was given. A thick mucoid secretion issued from Stenson's duct, followed by a profuse watery discharge. The gland was definitely decreased in size, but complete reduction to normal size was considered to be impossible, because of the fibrosis caused by the prolonged blockage of the duct. However, the patient has parotid secretion on the right side at present. The mouth ulcers healed promptly, and have not recurred.

Case 4. C. R., 52 year-old female, had a history of frequently recurring swelling of the left side of the face accompanied by pain in the same area just before eating. The swellings lasted from three to four weeks and spontaneously subsided giving the patient a great deal of discomfort during these intervals. The patient was seen by another physician in the clinic after having had her most recent attack for three weeks. She was to return the next week for a discussion of therapy. Just prior to her recent visit, she had a spontaneous evacuation of a thick mucoid secretion from Stenson's duct followed by a watery discharge. On her latest visit, the gland had returned to normal without medication of any sort.

#### COMMENT

The basis of this condition can be due to an infection of the parotid secretion probably in Stenson's duct. Since the parotid duct is a serous gland, it cannot produce under ordinary circumstances a thick mucoid material. However, it is conceivable that under certain conditions the secretory part of Stenson's duct can secrete a mucoid substance. Perhaps the reason for this may be an over-preponderant sympathetic stimulus. In any case, stimulating the sympathetic nerves of the submaxillary gland produces a thick mucoid saliva. It is possible that Emden's old theory of secretory neurosis has some basis.

Injection of prostigmine methylsulphate, a parasympathetic drug, is similar to stimulating the parasympathetic secretory nerves, and causes a profuse

prolonged outpouring of the thin serous parotid secretion. In doing this the thicker mucoid material is dislodged and eliminated, and is prevented from reforming, at least temporarily.

The treatment might be applicable also to extremely small salivary duct stones, but must be cautiously used. This seemed to be suggested by Patterson (7) who stated that many small stones can be made to pass from the hydrostatic pressure of the saliva behind them. If the treatment can be used in the early stages while the stone is still small, it may be able to prevent the formation of larger stones. It would seem wise to restrict this therapy to extremely small calculi, because of the danger of increased salivation in a duct blocked by a large parotid calculus.

Ballon and Ballon (8) quote one case in their article which would appear to fall in the class of obstruction coming under this therapy. A woman of 60 years had a submaxillary duct block which proved to be due to purulent secretion containing sand-like particles, which were removed by probing the duct.

Probing the duct either for diagnosis or treatment is not to be undertaken without some thought, as Walters (6) felt that the danger of perforation and spreading of an acute inflammatory process was an ever-present one. The therapy suggested in this article would obviate the necessity for probing, in certain cases at least.

#### SUMMARY

1. Four cases of salivary duct obstruction without stones were presented.

2. A method of treatment was outlined that proved effective in eliminating the distress in three of the patients. The fourth patient had a spontaneous evacuation of the obstruction before treatment was given.

#### REFERENCES

1. Gross, F. and Sclafoff, D.: Pathology and Clinic of the Salivary Stone Disease. *Brun's Beiträge zur klin. Chir.*, 155:275, April 9, 1932.
2. Howard, C. P.: "Diseases of the Salivary Glands." *Nelson's Living Medicine*, Vol. V, Chapter 2, p. 25, New York, Thomas Nelson & Sons.
3. Payae, R. T.: Sialography: Its Technique and Application. *British J. of Surg.*, 19:142, July, 1931.
4. Lewis, F. T. and Bremer, J. L.: A Textbook of Histology. 1927, Philadelphia, P. Blakiston's Son, p. 235.
5. Best, C. H. and Taylor, N. B.: The Physiological Basis of Medical Practice. Baltimore, William Wood & Co., p. 664, 1937.
6. Walters, C. H. A.: Sialolithiasis. *Canadian M. A. J.*, 30:533, May, 1934.
7. Patterson, R. H.: Salivary Gland and Duct Calculi. *Surgical Clinics of North America*, 12:335, April, 1932.
8. Ballon, H. C. and Ballon, D. H.: Salivary Calculi: Their Treatment by Catheterization and Dilatation of the Duct. *S. G. O.*, 64:226, Feb., 1937.

## Prothrombin and Fibrinogen Studies in Chronic Ulcerative Colitis\*

By

ROBERT C. PAGE, M.D.

and

Z. BERCOVITZ, M.D.

NEW YORK, NEW YORK

IN recent years the syndrome of chronic ulcerative colitis has come to be associated in men's minds with multiple vitamin deficiencies. Whether these deficiencies play any large part in the etiology of this disease still remains to be proved; however, some

think they constitute an essential part of the underlying mechanism (1).

Rectal bleeding is one of the earliest and most persistent symptoms of chronic ulcerative colitis. It follows that a study of some of the constituents of the clotting mechanism (prothrombin and fibrinogen) might be of assistance in explaining the rectal bleeding.

\*From the Gastro-Enterology Clinic, Department of Medicine, New York Post-Graduate Medical School and Hospital.  
Submitted July 15, 1942.

Prothrombin deficiency in chronic ulcerative colitis has been reported by many investigators, Mackie (2), Butt and Snell (3), Hult (4), Stewart and Rourke (5).

The patients included in this study were all outpatients who attended the clinic at regular intervals. They were all adults who had been diagnosed as having chronic non-specific ulcerative colitis from which they had suffered for more than six months. All of the patients were ambulant and were in a stage of remission, however, most of them had some diarrhea varying from two to eight bowel movements daily, often blood-streaked.

Prothrombin clotting time determinations and fibrinogen content of blood plasma were studied in these patients and also in a control group of healthy normal adults.

#### METHOD USED IN DETERMINING PROTHROMBIN CLOTTING TIME

The method used throughout this study was the

Quick method (6) modified by using Russell viper venom, instead of brain tissue extract, as the thromboplastic agent (7, 8). Four and one-half cubic centimeters of venous blood were drawn into a dry syringe and mixed with 10 mg. potassium oxalate in a centrifuge tube. The blood was centrifuged for five minutes at 1,500 r.p.m. and the oxalated plasma pipetted off. The prothrombin clotting time was done immediately or within two hours, and, if hemolysis was present, the sample was discarded.

The test was performed as follows: 0.2 cc. of oxalated plasma was pipetted into a small test tube (75 x 10 mm.), 0.2 cc. of Russell viper venom\* (1:10,000) solution was added. Calcium chloride solution (1.11% calcium chloride) 0.2 cc. was then added and the stopwatch immediately started. The tube was agitated for ten to fifteen seconds and tilted until separate, discrete fibrin particles formed which was taken as the end

\*Russell Viper Venom, "Stypven," supplied by Burroughs Wellcome & Co. (U. S. A.) Inc., New York, N. Y.

TABLE I

Data on prothrombin clotting times (in seconds) of twenty-one patients with chronic ulcerative colitis and a group of five normal adults.

| No. | WEEKLY INTERVALS |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      | Mean                   |
|-----|------------------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------------------------|
|     | 1                | 2    | 3    | 4    | 5    | 6    | 7    | 8    | 9    | 10   | 11   | 12   | 13   | 14   | 15   | 16   | 17   | 18   | 19   | 20   | 21   | Sec.                   |
| A   | 1                | 20.9 |      | 23.1 |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      | 22.0                   |
|     | 2                | 20.1 |      | 22.2 |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      | 21.2                   |
| B   | 3                | 26.0 |      | 32.0 |      | 36.6 |      | 38.8 |      |      |      | 26.4 |      |      |      |      |      |      |      | 24.0 |      | 30.6                   |
|     | 4                | 61.3 |      | 26.6 |      | 24.3 |      |      |      | 33.2 |      |      | 27.0 |      |      |      |      |      |      |      |      | 34.5                   |
|     | 5                | 30.3 |      |      | 29.0 |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      | 20.7                   |
|     | 6                | 38.2 | 26.2 |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      | 32.2                   |
|     | 7                | 32.7 | 26.7 |      |      |      |      |      | 27.0 |      |      |      |      |      |      |      |      |      |      |      |      | 28.8                   |
|     | 8                | 26.5 |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      | 28.3 |      |      | 27.4                   |
|     | 9                | 30.0 | 28.0 |      | 31.5 |      |      | 22.9 |      | 24.5 |      | 27.0 | 26.1 |      |      | 31.2 |      | 27.0 |      |      |      | 27.9                   |
|     | 10               | 26.2 |      |      | 31.2 | 28.4 | 29.5 |      |      | 29.2 |      | 33.2 |      |      |      |      | 23.7 |      |      |      | 26.0 | 28.4                   |
| C   | 11               | 19.5 |      |      | 25.7 |      | 27.8 |      | 25.3 | 24.5 |      | 24.4 |      | 24.3 |      | 28.8 |      |      |      | 19.2 |      | 24.9                   |
|     | 12               | 32.0 |      | 32.5 |      | 24.4 |      | 30.3 |      | 26.0 |      | 27.4 |      | 26.0 |      | 20.5 | 23.0 | 26.1 |      |      | 24.2 | 26.6                   |
|     | 13               | 25.0 |      |      |      | 19.6 |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      | 22.8                   |
|     | 14               | 25.5 |      |      |      |      |      | 22.7 |      |      | 26.0 |      |      | 27.5 |      |      |      |      |      |      |      | 25.4                   |
|     | 15               | 22.4 |      |      |      | 20.4 |      |      |      |      |      | 21.3 |      |      |      |      |      |      |      | 28.0 |      | 26.9                   |
|     | 16               | 26.2 |      | 23.0 |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      | 24.6                   |
|     | 17               | 22.5 |      | 21.8 |      |      |      |      |      |      |      | 25.0 |      | 23.7 |      |      |      | 24.2 |      |      |      | 23.4                   |
|     | 18               | 26.5 | 20.7 |      |      | 19.5 | 17.0 |      |      | 16.8 |      |      |      |      |      |      |      |      |      |      |      | 20.1                   |
|     | 19               | 26.9 |      |      |      | 32.1 |      | 23.9 |      |      | 27.6 |      |      | 24.7 |      |      |      | 20.1 |      |      |      | 25.9                   |
|     | 20               | 26.7 | 28.2 | 21.5 |      | 26.7 |      | 25.5 | 27.2 | 26.5 | 22.2 |      | 23.5 |      | 27.6 |      | 27.4 | 29.4 |      | 23.4 |      | 26.8                   |
|     | 21               | 30.1 | 27.2 |      |      |      |      | 25.4 |      | 23.5 |      |      |      |      | 25.8 | 26.6 |      |      |      |      |      | 26.1                   |
| D   | 1                | 20.9 | 19.1 | 17.8 |      | 17.6 |      | 19.9 |      | 19.6 |      | 21.4 |      | 20.3 |      | 21.0 |      |      |      |      |      | Mean 26.3 Sec.<br>19.7 |
|     | 2                | 21.1 | 18.2 | 21.2 | 18.8 | 18.3 | 20.7 | 20.5 |      | 19.4 |      | 21.2 |      | 19.5 |      | 21.2 |      | 20.4 |      | 19.9 |      | 20.3                   |
|     | 3                | 21.9 | 19.9 | 22.1 | 19.0 |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      | 20.6                   |
|     | 4                | 20.4 | 21.9 | 21.1 | 21.4 | 18.2 |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      | 20.6                   |
|     | 5                | 19.7 |      | 22.3 | 23.8 | 19.7 |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      | 21.4                   |

Mean 20.2 Sec.

- Group A—Two patients with prothrombin times within the normal range (less than 24 seconds, which corresponds to a prothrombin concentration of more than 70 per cent in the plasma).
- Group B—Six patients, with repeated prothrombin times greater than the upper limit of normal (more than 24 seconds, which corresponds to a prothrombin concentration of less than 50 per cent in the plasma), who were considered to have hypoprothrombinemia.
- Group C—Thirteen patients, with repeated prothrombin times varying from normal to prolonged, who were considered to have subclinical hypoprothrombinemia.
- Group D—Five healthy, normal adults, with repeated prothrombin times. All of the thirty-five prothrombin times were within the normal limits (less than 24 seconds).

point. All tests were done in triplicate and the average taken as the prothrombin clotting time.

The prothrombin clotting time in normal individuals using Russell viper venom has been found to be 20.76 seconds  $\pm 2.32$  seconds (9) and 19.5 seconds  $\pm 2.9$  seconds (10).

### RESULTS OF REPEATED PROTHROMBIN CLOTTING TIME DETERMINATIONS

Prothrombin clotting time of twenty-one patients with chronic ulcerative colitis and five normal adults were studied (Table I). Blood was taken in the early afternoon, and the prothrombin clotting time was determined. Blood was obtained at intervals of one to several weeks over a period of time ranging as high as twenty-one weeks. Two to eleven determinations were carried out on each patient. In all, 108 prothrombin determinations were made in the twenty-one patients with a mean clotting time of 26.32 seconds which corresponds to a prothrombin level of 65% (Table II). This is definitely in the hypoprothrombinemic range. On a statistical basis (9), there is only one chance in 100 that a prothrombin clotting time of 26 seconds (by the method used in this study) is normal. In some of the patients the prothrombin

TABLE II

*Statistical analysis of 108 prothrombin clotting times in patients with chronic ulcerative colitis and of 26 normal adults.*

|                                | Normal     | Chronic Ulcerative Colitis |
|--------------------------------|------------|----------------------------|
| Number of Cases                | 26         | 21                         |
| Mean prothrombin clotting time | 20.76 sec. | 26.32 sec.                 |
| Standard deviation             | $\pm 2.32$ | $\pm 7.45$                 |
| Minimum                        | 15.4       | 16.8                       |
| Maximum                        | 25.0       | 61.3                       |

clotting time varied from week to week. In one instance the variation was as high as 37 seconds. This, however, was unusual. The others varied from 1 to 12 seconds. Twenty-seven of the 108 determinations can be considered in the normal range, that is, less than 24 seconds. Of the 21 patients studied only two (9.5%) had repeated prothrombin determinations within the normal range (Group A, Table I). The other 19 had prothrombin clotting times that allowed them to be put into two groups. Six patients (28.5%) had repeated tests that were all above the normal range and therefore these can be classified as having a constant hypoprothrombinemia (Group B, Table I). Thirteen patients (61.9%) fluctuated between normal and elevated prothrombin clotting times and can be classified as having a borderline or subclinical hypoprothrombinemia (Group C, Table I). This latter group would be a source of error if only one determination of prothrombin clotting time had been made.

The marked variation between repeated prothrombin times in the patients with chronic ulcerative colitis led us to do repeated prothrombin times in normal adults (Table I). Thirty-five prothrombin times were done on five normal adults with a mean value of 20.2 seconds. This corresponds closely to a mean pro-

thrombin time of 20.76 seconds obtained in twenty-six normal adults previously reported by one of us (9). The variation between the repeated prothrombin times in normal adults was much smaller than obtained in the patients with chronic ulcerative colitis. It may therefore be assumed that the major part of the variation in repeated prothrombin times was due to changes in prothrombin blood level in the patient rather than to variations in the method employed.

An analysis of variance (Table III) was carried out

TABLE III

*Analysis of variance of prothrombin clotting times in patients with chronic ulcerative colitis.*

| Source of Variation | Degree of Freedom | Sums of Squares | Mean Square | Standard Deviation |
|---------------------|-------------------|-----------------|-------------|--------------------|
| Total               | 63                | 2397.68         |             |                    |
| Between patients    | 17                | 943.44          | 55.4965     | 7.45               |
| Within patients     | 46                | 1454.19         | 31.6128     | 5.62               |

to determine if the variation of the prothrombin time in the same patient on repeated determinations is as great as between different patients. The standard deviation for values obtained in the same patient was 5.62. This value is almost as great as the standard deviation of 7.45 which is a measure of the variation between individuals. In other words one can expect almost as much variation in repeated determinations on the same patient as between patients.

### DISCUSSION

From the data presented it would appear that hypoprothrombinemia is relatively common in patients with chronic ulcerative colitis (Fig. 1). Six of twenty-one patients had a constant increase of the prothrombin clotting time in repeated tests. In thirteen the prothrombin clotting time varied from normal to increased. Because of the great variation of the prothrombin clotting times of the patients studied, it is essential that repeated determinations be made in patients with chronic ulcerative colitis before they can be classified as having a normal or decreased blood prothrombin level.

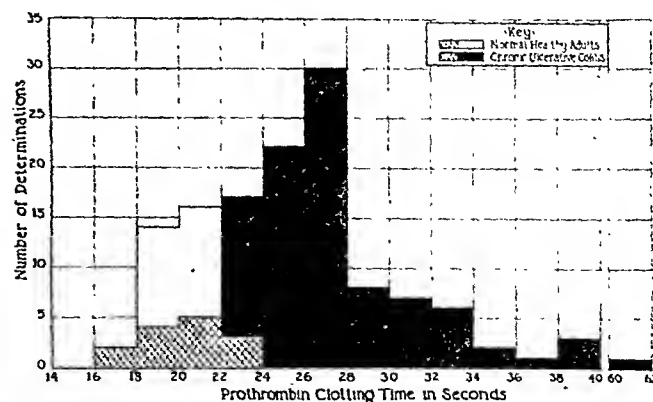


Fig. 1. Frequency distribution of 108 prothrombin clotting times in a group of 21 patients with chronic ulcerative colitis and 35 prothrombin clotting times in 5 normal healthy adults.

These findings suggest that several factors may have been present, namely, inadequate amounts of Vitamin K or its antecedents in the food ingested, faulty absorption from the intestinal tract, and increased loss of Vitamin K in the presence of diarrhea.

#### FIBRINOGEN DETERMINATION IN BLOOD PLASMA

The method used for the fibrinogen content of blood plasma was a combination of the methods of Howe (11), Wu (12) and Koch and McMeekin (13) as adopted in the Biochemical Laboratories of the Philadelphia General Hospital. It consists in adding 1 cc. of oxalated plasma to 48 cc. physiologic saline and adding 1 cc. 2.5% calcium chloride, mixing and letting it stand for 30 minutes. The clot was removed, dried

TABLE IV

Results of study of plasma fibrinogen levels in normal adults and eleven patients with chronic ulcerative colitis

|                            | Patients Studied<br>Number of | Maximum | Minimum | Mean   |
|----------------------------|-------------------------------|---------|---------|--------|
| Normal adults              | 13                            | 0.38%   | 0.19%   | 0.282% |
| Chronic ulcerative colitis | 11                            | 0.53%   | 0.28%   | 0.370% |

and placed in an ignition tube with 1 cc. of acid digestion mixture. Five drops of caprylic alcohol were added to prevent foaming. The mixture was boiled vigorously and when white fumes appeared, superoxol (30%  $H_2O_2$ ) was added to clear the solution (about 0.5 cc.). The solution was again heated vigorously and then cooled. Distilled water was added to make a total volume of 35 cc. Fifteen cubic centimeters of Nessler's solution were then added, the solution was centrifuged and the supernatant fluid was matched against standards containing from 0.6 mg. to 1.0 mg. of nitrogen. The normal range for plasma fibrinogen with this procedure is 0.2% to 0.4%.

Thirteen healthy, normal adults and eleven patients with chronic ulcerative colitis were studied as to plasma fibrinogen level. The results for the normals

falls within the normal limits 0.2% to 0.4% except for one determination which was 0.19%. Of the eleven patients with chronic ulcerative colitis eight had plasma fibrinogen levels within the normal range and three had levels above the upper limit of normal (0.4%). The mean for the chronic ulcerative colitis patients was 0.370% while for the normals it was 0.282% so that it can be stated with reasonable certainty that the plasma of patients with chronic ulcerative colitis contains somewhat more fibrinogen than normal adults (Table IV).

The slight increase of fibrinogen in chronic ulcerative colitis is probably explained by the fact that inflammatory and destructive lesions of any kind are the normal stimulus to fibrinogen production (Foster and Whipple (14)) and it follows that the colonic pathology present in chronic ulcerative colitis stimulates the liver to increase its production of fibrinogen.

#### SUMMARY

Twenty-one patients with chronic ulcerative colitis were studied to determine the prothrombin clotting time over periods up to twenty-one weeks.

Six patients (28.5%) had a constant hypoprothrombinemia. Thirteen patients (61.9%) fluctuated between normal and elevated prothrombin clotting time and can be classified as having a borderline hypoprothrombinemia. Two patients (9.5%) had repeated prothrombin clotting times within the normal range.

More than one prothrombin clotting time must be determined on the same patient with chronic ulcerative colitis since the prothrombin time for such individuals varies widely from week to week.

From the data presented it would appear that hypoprothrombinemia may be more frequent than is supposed in patients with chronic ulcerative colitis.

Eleven patients with chronic ulcerative colitis were studied as to plasma fibrinogen content.

Plasma of patients with chronic ulcerative colitis contains somewhat more fibrinogen than normal adults.

The only alteration in the blood clotting mechanism in chronic ulcerative colitis would appear to be a frequent occurrence of a low blood prothrombin level and this may explain some of the continued rectal bleeding that occurs in this disease.

#### REFERENCES

1. Mackie, T. T.: "Ulcerative Colitis. II. Deficiency States." *J. A. M. A.*, 104:175, 1935.
2. Mackie, T. T.: "Vitamin K Deficiency in the Absence of Jaundice." *New York State J. Med.*, 50:987, 1940.
3. Butt, H. R. and Snell, A. M.: "Vitamin K." p. 96. W. B. Saunders Co., Philadelphia, 1941.
4. Hult, H.: "Om K-Avitaminosis." *Nord. med.*, 4:3627, 1939.
5. Stewart, J. D. and Rourke, G. M.: "Prothrombin and Vitamin K Therapy." *New England J. Med.*, 221:403, 1939.
6. Quick, A. J.: "The Nature of the Bleeding in Jaundice." *J. A. M. A.*, 110:1658, 1938.
7. Fullerton, H. W.: "Estimation of Prothrombin: Simplified Method." *Lancet*, 2:195, 1940.
8. Page, R. C. and Russell, H. K.: "Prothrombin Estimation Using Russell Viper Venom." *J. Lab. and Clin. Med.*, 26:1366, 1941.
9. Page, R. C., de Beer, E. J. and Orr, M. L.: "Prothrombin Studies Using Russell Viper Venom. II. Relation of Clotting Time to Prothrombin Concentration in Human Plasma." *J. Lab. and Clin. Med.*, 27:197, 1941.
10. Shapiro, S., Sherwin, B., Redish, M. and Campbell, H. A.: "Prothrombin Estimation: A Procedure and Clinical Interpretations." *Proc. Soc. Exper. Biol. and Med.*, 50:85, 1942.
11. Howe, P. E.: "Determination of Protein in Blood—A Micro Method." *J. Biol. Chem.*, 49:169, 1921.
12. Wu, H.: "A New Colorimetric Method for the Determination of Plasma Protein." *J. Biol. Chem.*, 51:33, 1922.
13. Koch, S. C. and McKeekin, T. L.: "A New Direct Nesslerization Micro-Kjeldahl Method and a Modification of the Nessler-Folin Reagent for Ammonia." *J. Am. Chem. Soc.*, 46:2066, 1924.
14. Foster, D. P. and Whipple, G. H.: "Blood Fibrin Studies." *Am. J. Physiol.*, 58:407, 1922.

## Studies on Colon Irritation

### III. Bulk of Feces

By

OSKAR WOZASEK, M.D.

and

F. STEIGMANN, M.S., M.D.

CHICAGO, ILLINOIS

**W**HETHER abnormalities of the bowel movement such as occur in constipation, may be per se sufficiently irritant to produce pathology in the bowel, has been much discussed. Since a minority, only of constipated people develop signs of mucous colitis, it was assumed that constipation leads to colitis only when other predisposing factors are present. Nevertheless, constipation is a frequent finding in mucous colitis (1). Certain diets and laxatives frequently used in the management of constipation also may be held responsible for the development of "colitis" just as is constipation itself. Thus, constipation may be a causal, contributive, or a resulting factor in colitis.

Because mucous colitis is often found in individuals with a nervous disposition, the term "irritable colon" was suggested as more descriptive for such a condition (2, 3). That the early recognition of colon irritation would be helpful for the causal analysis and the management of such patients before a vicious cycle has been established will be admitted.

For the differential diagnosis of colonic disturbance, especially the recognition of etiologic causes, chemical and microscopic examinations of the stools and bowel discharge, have been elaborated and tested clinically by us. In the course of this work it became apparent that in many normal people, abnormal constituents were found in the feces in association with an abnormal bowel movement (constipated—hard, or diarrheal—watery stool) (4).

Clinical criteria for the evaluation of the bowel habit are the frequency of evacuation, and the shape, appearance and consistency of the feces: 100-200 grams of feces in 24 hours with a moisture content of 65-67 per cent is considered normal. Sufficient bulk of feces is considered necessary for the maintenance of a coordinated function of the gastro-intestinal tract.

The most important bulk-forming constituents in the daily diet of man are cellulose-containing foods as shown in the fundamental work of Rubner (5-8). A stool small in bulk may be due to a low residue diet, possibly to over-absorption (greedy colon) and may be found also in cases of spastic colon and in mucous colitis.

We have studied the question of a direct relation between signs of colon irritation and constipation. The mere clinical statement "constipation" is not sufficiently significant. Single bowel evacuations of each individual were studied over a period of time. Bran was given in every case to test the individual reaction

toward a bulk-forming substance. In the selection of the material we considered constipation as ranging between normal and diseased states, as well as the fact that early signs of irritation must be studied.

#### MATERIAL AND METHODS

*Group I:* In 45 supposedly normal individuals, (table group I) single stool specimens were collected over a period of 11 days. The 3 days in the beginning and at the end were used for controls. During the 5 intervening days one ounce of bran was added to the normal daily diet. The weight of each stool was recorded, and the dry matter determined. Chemically, the specimens were tested for mucous secretion and proteins. Smears, stained with carmin and Giemsa stains, were examined microscopically for mucous secretion, mucous strings and cells.

*Group II:* Fifty-eight out-clinic patients who complained of various abdominal symptoms and most of whom considered themselves constipated, were similarly studied and stool examinations performed in an identical way.

#### RESULTS AND DISCUSSION

None of the normal subjects (Group I) complained of abdominal distress or was conscious of abnormal bowel movement during the experimental period. Nevertheless, there were widely ranging variations in the frequency of bowel movements, consistency and weight of stool specimens which, however, were still within physiologic limits. The average weight of feces per day during the control periods in 30 cases was 115 grams. In 15 cases (33%) the daily average was at no time higher than 75 grams; the average value was about 52 grams. The low daily average in these latter cases was not due to infrequent movement; *each single stool specimen was low in weight*. In some of these cases we were able to control this finding over a period of several months and observed this "tendency to low bulk" all the time.

In 13 of the 15 cases (86%) with low bulk, ingestion of bran resulted in a marked increase of the total weights, as well as of the dry matter, while in the first 30 individuals with normal bulk there was an increase in only 16 instances (53%), in 10 no marked change, and in 4 a decrease of the stool weights.

The quantitative determination of mucous substances in the feces and the microscopic examination confirmed our previous observations that mucous secretion in the feces shows physiologic limits (up to 0.1 cc. 1 gr. feces) and that higher values indicate hypersecretion (4).

In a number of individuals who were observed over

\*From the Department of Pharmacology and Therapeutics and Internal Medicine, University of Illinois College of Medicine, Chicago, Illinois.

Aided by a grant from the Kellogg All-Bran Company.  
Submitted July 15, 1942.



a period of several months, hypersecretion was constantly present at every re-examination. Similarly, in a number of individuals the appearance of stringy particles or lumpy mucus was observed repeatedly at microscopic re-examinations. In these, however, the relation of these findings to an abnormal bowel movement was quite obvious. Increased mucous secretion, mucous strings (membranes) or both at the same time or alternating, were found in 15 out of 45 cases (33%) already in the preliminary examination. However, of the 15 cases who showed a tendency to low bulk stools, 8 (53%) had abnormal findings; while of the 30 cases with normal stool weights, only 7 (23%) had abnormal stool constituents.

No major gastro-intestinal or other abdominal disease was found in the 58 cases of the second group (Group II). All of them, however, had various complaints such as distress, flatulence, belching, or gas

eructation. Most of them considered themselves constipated. In a number of cases, a careful check could not confirm the autodiagnosis of constipation. In fact, 14 cases of this group showed loose and even frequent movements. Changes in bulk and consistency, and infrequent evacuations were noted more often in this group. However, the average stool weights in 35 cases were 108 grams which is about the same as in the normal bulk subjects of Group I (114 grams). Of these 35 cases twenty (57%) showed an increase in stool weights while eating bran. However, compared with the same cases of the normal group the increase in bulk was less marked, and in the average not higher than 24 per cent. Twenty-three cases (40%) revealed constant low stool weights with an average of 50 grams. Of these cases with low bulk only 14 (61%) showed marked increase in stool weights during the bran week. Increased mucus values or microscopic

TABLE I  
Group I—45 normal subjects

|  | Number<br>Subjects<br>Tested | Periods                           | Average Weight of Feces<br>in Gm. Per Day |             |                         |             | No. Cases<br>Showing<br>Mucous<br>Secretion<br>Exceeding<br>0.1 cc. Per<br>1 Gm. Stool | No. Cases<br>Showing<br>Microscopic<br>Carmin<br>Positive<br>Strings or<br>Membranes | No. Cases<br>Showing<br>Both<br>Increased<br>Mucus and<br>Microscopic<br>Strings |
|--|------------------------------|-----------------------------------|---|-------------|-------------------------|-------------|--|--|--|
|  |                              |                                   | Total Weight                              |             | Dry Matter              |             |  |  |  |
| 1. Group with Normal Bulk—30                             |                              |                                   |   |             |                         |             |  |  |  |
| A. Subjects with increased<br>bulk during bran ingestion | 16                           | Preliminary<br>Bran<br>After bran | 97<br>148<br>98                           | Inc.<br>53% | 23.61<br>32.49<br>22.85 | Inc.<br>38% | 1<br>3<br>2  | 0<br>2<br>1  | 2<br>0<br>0  |
| B. Subjects with decreased<br>bulk during bran ingestion | 4                            | Preliminary<br>Bran<br>After bran | 148<br>103<br>92                          | Dec.<br>30% | 29.96<br>24.00<br>22.13 | Dec.<br>29% | 0<br>0<br>0  | 0<br>0<br>0  | 1<br>0<br>1  |
| C. Subjects with unchanged<br>bulk during bran ingestion | 10                           | Preliminary<br>Bran<br>After bran | 128<br>126<br>78                          |             | 30.17<br>31.15<br>19.42 |             | 0<br>1<br>0  | 0<br>2<br>1  | 3<br>0<br>2  |
| 2. Group with Low Bulk—15                                |                              |                                   |   |             |                         |             |  |  |  |
| A. Subjects with increased<br>bulk during bran ingestion | 13                           | Preliminary<br>Bran<br>After bran | 50<br>85<br>58                            | Inc.<br>70% | 14.65<br>22.17<br>14.13 | Inc.<br>51% | 4<br>3<br>5  | 2<br>2<br>1  | 2<br>1<br>1  |
| B. Subjects with decreased<br>bulk during bran ingestion | 2                            | Preliminary<br>Bran<br>After bran | 65<br>51<br>41                            | Dec.<br>22% | 10.27<br>13.58<br>10.53 | Inc.<br>32% | 0<br>0<br>0  | 0<br>1<br>1  | 0<br>0<br>0  |

Group II—58 abnormal subjects

|  |    |                                   |                   |              |                         |             |             |             |             |
|--|----|-----------------------------------|-------------------|--------------|-------------------------|-------------|-------------|-------------|-------------|
| 1. Group with Normal Bulk—35                             |    |                                   |                   |              |                         |             |             |             |             |
| A. Subjects with increased<br>bulk during bran ingestion | 20 | Preliminary<br>Bran<br>After bran | 104<br>139<br>101 | Inc.<br>34%  | 22.89<br>30.24<br>21.06 | Inc.<br>32% | 3<br>3<br>5 | 0<br>1<br>0 | 3<br>1<br>2 |
| B. Subjects with decreased<br>bulk during bran ingestion | 7  | Preliminary<br>Bran<br>After bran | 150<br>117<br>117 | Dec.<br>22%  | 37.43<br>27.03<br>29.53 | Dec.<br>28% | 1<br>1<br>2 | 2<br>2<br>1 | 0<br>0<br>0 |
| C. Subjects with unchanged<br>bulk during bran ingestion | 8  | Preliminary<br>Bran<br>After bran | 134<br>134<br>125 |              | 24.32<br>22.66<br>27.26 |             | 2<br>1<br>2 | 1<br>1<br>1 | 0<br>0<br>0 |
| 2. Group with Low Bulk—23                                |    |                                   |                   |              |                         |             |             |             |             |
| A. Subjects with increased<br>bulk during bran ingestion | 14 | Preliminary<br>Bran<br>After bran | 46<br>94<br>57    | Inc.<br>104% | 14.19<br>21.31<br>19.29 | Inc.<br>50% | 4<br>3<br>1 | 3<br>4<br>2 | 0<br>0<br>2 |
| B. Subjects with decreased<br>bulk during bran ingestion | 4  | Preliminary<br>Bran<br>After bran | 52<br>33<br>64    | Dec.<br>37%  | 12.84<br>9.53<br>17.79  | Dec.<br>26% | 0<br>1<br>0 | 0<br>1<br>1 | 0<br>0<br>0 |
| C. Subjects with unchanged<br>bulk during bran ingestion | 5  | Preliminary<br>Bran<br>After bran | 62<br>57<br>71    |              | 18.34<br>16.64<br>12.39 |             | 2<br>2<br>3 | 0<br>0<br>0 | 0<br>0<br>1 |

Inc. = increase  
Dec. = decrease

strings were found in 21 (36%) of all the cases in this group.

Leucocytes in stool smears in any considerable number which is an indication of inflammation, or the presence of protein in feces which is an indication of bleeding or ulceration of the colon, were not found in any of the cases of either group.

In none of the cases of this study did we find any considerable gross mucus, either in loose form or as ribbons or strands; although a number of the out-clinic patients dated their symptoms over a long period of time.

Increased mucous secretion values were typical findings in certain individuals, and one may assume that they express a state of hypersecretion or a disposition to it. A constant and typical relation of the findings to constipation, although often present, could however, not be proved. A relation between the findings of mucomembranous particles shown by microscopic examination and abnormal bowel movements was, however, quite obvious, and here low bulk plays a considerable part.

A careful study convinces us that there is a tendency to low bulk in a comparatively large number of supposedly normal individuals. Since none of them consciously used a particularly low residue food, one may assume that it is a constitutional sign in these individuals. It may seem remarkable that bran effected an increase in stool weights in these cases more often than it did in cases with normal bulk. As to the observation of signs of irritation our experience gives us the impression that they occur in these individuals secondary to the abnormal bowel movement. In the group with abdominal and general complaints, low bulk cases were seen in about the same percentage as in the normal group. A bulk producing effect of bran was observed less often in the group with abdominal complaints. Signs of irritation were found in individuals of both groups in a comparatively high percentage. They were almost exclusively observed in certain individuals who showed this finding also in the preliminary examination and on various days during a longer observation period, though not constantly. It

seems, however, of interest that the percentage of individuals who showed these signs was not lower in the normal than in the group with abdominal symptoms.

## SUMMARY

The bowel movement of 45 normal and 58 individuals with abdominal complaints were studied. Stools were examined for the effect of bran on the bowel movements, and for signs of colon irritation.

Constant low stool weight (tendency to low bulk) was observed in 33 per cent of the normal and in 40 per cent of the individuals with abdominal complaints.

A bulk increasing effect of bran among individuals with constant low stool weights was seen in 13 out of 15 subjects (86%) of the normal group, and in 14 out of 23 (61%) of those of the group with abdominal symptoms. Of the 30 cases with average normal stool weights, there was a bulk increasing effect of bran in 16 cases (53%) of the normal group. In the group with abdominal symptoms, 35 had normal average weights; of these 20 (57%) had increased bulk after bran.

Increased mucous secretion or abnormal microscopic mucous findings were found in 15 of 45 cases (33%) of the normal subjects and in 21 of 58 cases (36%) of those who had abdominal complaints. Comparing the cases with low bulk, we found increased mucous secretion or microscopic abnormal findings in 8 of 15 cases (53%) in the normal group and in 9 of 23 (39%) in the group who had abdominal symptoms.

## REFERENCES

1. Friedenwald, J., Feldman, M. A. and Rosenthal, L. J.: Mucous Colitis Observations in 500 Cases. *Ann. Int. Med.*, 3:521-544, Dec., 1929.
2. Jordan, S. M. and Kiefer, E. D.: The Irritable Colon. *J. A. M. A.*, 93:592-594, Aug., 1929.
3. Bockus, H. L. and Willard, J. H.: The Irritable or Unstable Colon. *Nebr. State Med. J.*, 9:321-326, Sept., 1933; 10:375-376, Oct., 1933.
4. Fantus, B., Wozasek, O. and Steigmann, F.: Studies on Colon Irritation. *Am. J. Dig. Dis.*, 8:295-300, No. 8, Aug., 1941.
5. Bassler, A.: Diseases of the Digestive System. F. A. Davis Co., Philadelphia, 3rd Ed., 2:146, 1932.
6. Todd, T. C. and Sanford, A. H.: Clinical Diagnosis by Laboratory Methods. W. B. Saunders, Philadelphia and London, 428, 1931.
7. Borgstrom, St.: Studien über den nahrungsphysiologischen Wert der Weizenkleie unter besonderer Berücksichtigung der Bedeutung der Erhitung. *Acta physiol. Scand.*, 2: supplement 7, 1941.
8. Fantus, B. and Hirschberg, N.: The Mode of Action of Bran II. *Rev. of Gastro-Enterol.*, 8:277-280, July, Aug., 1941.

# Serum Diastase Determinations During Artificially Produced Intra-Duodenal Pressure Against the Head of the Pancreas\*

## Preliminary Report

By

S. G. CASTIGLIANO, M.D.  
PHILADELPHIA, PENNSYLVANIA

## SERUM DIASTASE

THE development of more accurate methods for the microestimation of the diastase level in blood and urine has led to its use in the diagnosis of pancreatic disease. Serum and urine diastase determinations are of greatest value in differentiating acute pancreatitis from other acute abdominal episodes. It has been established that obstruction of the pancreatic ducts or

any disturbance which causes a passage of pancreatic enzymes into the blood and lymph results in a marked rise in serum diastase (1). The rise of serum diastase in acute pancreatitis is thus explained. This rise usually takes 2 to 3 days to attain a maximum height; the diastase level then gradually returns to normal in from 10 to 14 days (2). The value of this diagnostic procedure is limited by the transient elevation followed by a rapid return to normal.

Obviously, diastatic determinations are of little or

\*American Oncologic Hospital, Philadelphia, Pa.  
Submitted Aug. 1, 1942.

no aid in determining pancreatic dysfunction in certain conditions, such as chronic pancreatitis, neoplasms, or even acute pancreatitis when seen some days after the onset.

Thus far a satisfactory test for pancreatic function is not known. Comfort, of the Mayo Clinic, in 1936 states that the serum lipase test has proved of greater value in the diagnosis of acute and subacute inflammation of the pancreas than any other procedure used (3). He recently re-emphasizes this point, and shows the serum lipase to be elevated in all the cases of chronic pancreatitis he studied (4). The enzyme concentration test performed by duodenal drainage in chronic pancreatitis has its advocates. It may be said, nevertheless, that a satisfactory functional test which can demonstrate relatively lower grades of pancreatic dysfunction is not known.

It has been predicted that some day a dye may be discovered which will be specifically eliminated by the pancreas. More than 100 dyes have been studied in Ivy's laboratory and none was found practical. A feasible test which could show abnormal function in a chronically diseased pancreas would be of considerable clinical value.

Appreciating the limitations of the ordinary procedure of examining the serum diastase level, McCaughan has attempted an improvement of the test, whereby, disease of the pancreas might be determined following acute episodes and in the more silent diseases of the pancreas, such as interstitial pancreatitis, neoplasm, and so forth.

The principle of McCaughan's test which I shall describe briefly is based on experiments performed on dogs.

A dog was anaesthetized and the stomach surgically approached. A rubber balloon was introduced through an incision in the stomach wall and placed in the duodenum just beyond the pyloric ring. The balloon was distended with water to a pressure of 90 mm. Hg. Oxalated blood samples were taken at intervals and the diastase concentrations determined. In 2 experiments performed by McCaughan the diastase showed a rise of 250% in one animal and 380% in the other, the distended balloon having been left in situ for 1 hour and 1½ hours respectively. Controls showed no elevation with a collapsed balloon in the duodenum. Another control animal, in which the common duct had been ligated to exclude the possibility of coincident biliary obstruction, showed a rise of only 150% in 2 hours. The pancreatic ducts of a dog were then ligated as a preliminary procedure and time allowed for the development of atrophy and fibrosis in the gland. The experiment of occluding the pancreatic duct openings by means of the distended balloon was then repeated. No rise in serum diastase was noted.

McCaughan states that clinical application of these observations has not yet been made, but suggests that an index to pancreatic function could be obtained. A normal pancreas might be expected to show a certain rise in the serum diastase after temporary obstruction by the balloon, whereas, the serum diastase in cases of disease of the pancreas might remain unaltered (6).

I have had the opportunity of applying McCaughan's procedure to a patient suffering with a *gumma* of the head of the pancreas, and, inasmuch as the tests have not previously been attempted on human subject, a description of my technique and results are given:

The patient, a jaundiced, poorly nourished, white

female, aged 34, was referred to this clinic for roentgen therapy to the pancreas. A diagnosis of carcinoma of the head of the pancreas had been made elsewhere after a laparotomy revealed a large mass situated in the head of the pancreas. The tumor was biopsied.

Our studies suggested that the definitely palpable mass in the epigastrium might be a *gumma*. Dr. J. McFarland, after microscopic study of the biopsy specimen, made a diagnosis of chronic granuloma. The blood Wasserman reaction was 4 plus. The patient was given the benefit of a therapeutic test, consisting of low doses of arsphenamine and massive doses of saturated solution of potassium iodine. She

CHART I

| Pressure      | Time           | Urine Diastase | Serum Diastase |
|---------------|----------------|----------------|----------------|
| None          | For 30 Minutes | 32 Units       | 8 Units        |
| 42-48 mm. Hg. | For 30 Minutes | 16 Units       | 16 Units       |
| 42-48 mm. Hg. | For 1 Hour     | — *            | 8 Units        |
| 42-48 mm. Hg. | For 1½ Hours   | 16 Units       | 32 Units       |

This test was performed while patient was under treatment. Mass in pancreas still palpable. Normal serum diastase value—16-32 units.  
\*No urine obtained.

rapidly improved. The tumor could no longer be palpated and roentgen studies showed that the previously noted indentation of the stomach had disappeared and the wide sweep of the duodenum had returned to normal. As a detailed case history is not necessary for the purpose of this paper, no further description will be given.

Preferably the test should have been done early during the course of the patient's illness and repeated after the patient showed marked improvement. Ideal as such an approach would have been, the patient's serious condition during her first admission precluded performing a strenuous experiment. The patient was discharged to the care of her home town physician and

CHART II

| Pressure      | Time           | Urine Diastase | Serum Diastase |
|---------------|----------------|----------------|----------------|
| None          | For 30 Minutes | 8 Units        | 8 Units        |
| 42-48 mm. Hg. | For 30 Minutes | — *            | 256 Units      |
| 42-48 mm. Hg. | For 30 Minutes | — *            | 128 Units      |

Test was repeated 9 weeks later. The patient had gained 16 pounds and felt entirely well. Note elevation of serum diastase at 30 minutes.  
\*No urine obtained.

because of financial reasons failed to return as advised. On the patient's return to the clinic, definite improvement was noted. The test was first performed at this time. (See Chart I). The test was repeated 9 weeks later when the patient appeared to be entirely well, had gained 16 pounds in weight and the epigastric mass was no longer palpable. (See Chart II).

### THE TEST

A diastase determination\* was done before passage of tube. The tube (see Figs. 1-5) was introduced

\*Winslow Method of Diastase Determination—from R. B. H. Gradwohl M.D., Second Edition, C. V. Mosby Co., 1938. Clinical Laboratory Methods and Diagnosis.

orally in the same manner as is done in a biliary drainage. A roentgenogram showed the tube to be properly situated. The tube was left in situ for 1 hour without increasing pressure to check the effect of the tube alone in the duodenum. The distention of the balloon by the injection of 200 cc. of water did not register resistance on the manometer. Because of the absence of registered pressure it was felt that the balloon could not be in the duodenum. The patient at this point was complaining of marked pulsations in the abdomen similar to those she experienced before treatment of the gumma. This was due, no doubt, to the pulsation of the aorta pulling rhythmically on the balloon-distended bowel as it passed under the crotch made by the superior mesenteric artery. The fluoroscope showed the tip of the tube to have passed into the jejunum. One hundred and fifty cc. of water were withdrawn and replaced with 5% sodium iodide. The fluoroscope revealed the balloon, now radio-opaque, to be almost entirely in the jejunum. Under fluoroscopic control, traction was applied to the Jutte tube in an effort to place the balloon in the second portion of the duodenum. The effect of this traction could be seen in the X-ray as the tube no longer followed the greater curvature of the stomach, but took a more direct

route to the cardia. This effort was unsuccessful as the balloon slipped by the pyloric sphincter into the stomach. The patient was rested as she was made markedly uncomfortable by the procedure. The experiment was attempted again. Only by careful, constant guidance and observation was the distended balloon kept reasonably close to the correct position, that is, the second portion of the duodenum. (See Fig. 6). Peristalsis becomes active and tends to propel the balloon onward. The pressure in this experiment was maintained at between 42-48 mm. Hg. pressure. The experiments of McCaughan were performed using a pressure of 90 mm. Hg. The pressure is of little significance, as it depends largely on the elasticity of the material used in the balloon. When an ordinary condom is used, pressure above 50 mm. Hg. apparently contributes no more actual tension against the head of the pancreas, as the balloon expands at the point of least resistance, that is, forward. (See Fig. 6, showing balloon distended far beyond the tip of the tube). Samples of blood and urine were taken before distention of balloon, and 30, 60 and 90 minutes after distention of balloon. (See Chart I). The test was

Fig 1

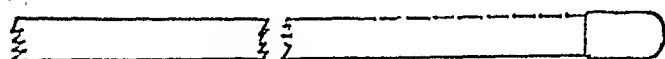


Fig 2



Fig. 1. Represents ordinary Jutte tube.

Fig. 2. A diagrammatic cross-section of a Jutte tube showing an adapter A inserted through the aperture indicated by arrow. The adapter is necessary to prevent the collapse of the tube.

Fig 3



Fig 4

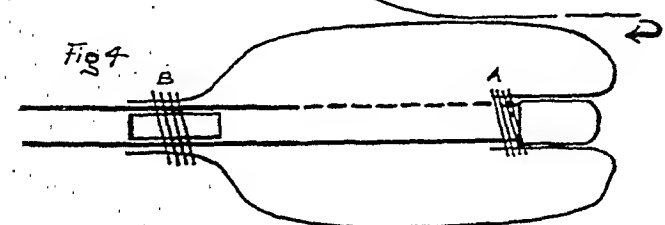


Fig. 3. The condom A is applied on the end of the Jutte tube just as it is with a Miller-Abbott tube. For the performance of the test described here a Miller-Abbott tube not only is unnecessary, but cumbersome.

Fig. 4. The condom tied at A, is evaginated and tied at B, producing an air-tight balloon. The adapter A described in Fig. 2 is situated at point B.

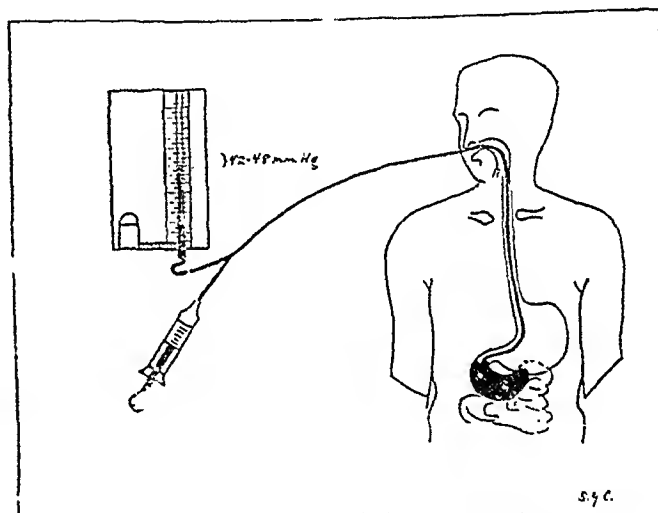


Fig. 5. Schematic drawing which shows simplicity of the apparatus. The tube is in situ with balloon distended by radio-opaque medium. Tube is connected with manometer and syringe.

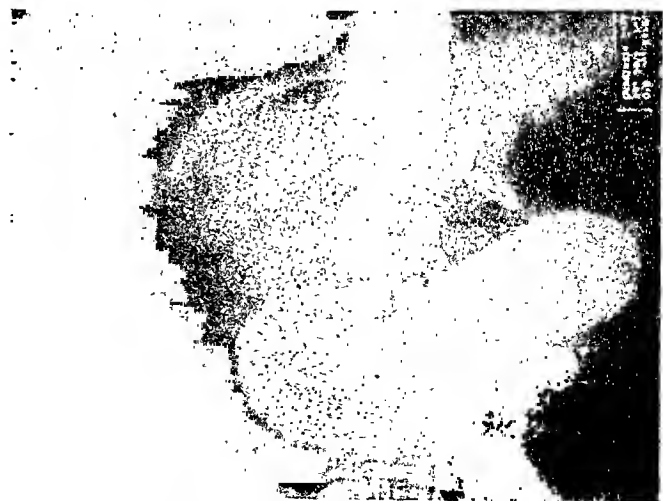


Fig. 6. Balloon filled with radio-opaque solution in proper position.

repeated 2 months later when the patient appeared perfectly well and had gained 16 pounds weight. (See Chart II).

### DISCUSSION

The results of the first test (see Chart I) show no rise in diastase, indicating, according to McCaughan, pancreatic dysfunction. The patient at this time, although not well, was clinically improved. The results of the second test (see Chart II) show a marked rise in diastase level, indicating, according to McCaughan, a normal pancreatic function. At this time patient felt perfectly well.

McCaughan's test or some modification of it may prove of value in studying pancreatic disease. Ingenious as this procedure appears to be, it has many shortcomings.

Firstly, this procedure is not as simple as McCaughan's description would lead one to believe. As I have pointed out, care is necessary to make certain that the balloon is in the proper position. This can be accomplished only by the use of a radio-opaque solution and frequent fluoroscopic visualization.

Secondly, the procedure is not without discomfort to the patient. Only a docile or extremely cooperative subject would submit to its continuance. It should not be used in acutely ill patients.

Thirdly, the development of this test has been suggested as an aid in the diagnosis of non-acute or chronic conditions of the pancreas. It remains to be seen whether variable degrees of pancreatic insufficiency can be determined by this method. Little is known about the so-called factor of safety of the pancreas. This factor of safety probably has to be de-

stroyed before dysfunction can be apparent. Furthermore, a moderate rise in diastase occurs with obstruction of the common duct, and also in hepatic disease per se. In other words, it is possible that this test, if fundamentally sound, may be of value only in cases where pancreatic function is considerably impaired.

### SUMMARY

1. Experience with serum diastase determinations on a human, following the method of McCaughan, is described for the first time.

2. It is not the purpose of this paper to weigh the merits of the procedure as an aid in clinical diagnosis, as sufficient work has not been done. The experimental results in one patient indicate, however, the possibility that the test may be fundamentally sound.

3. Despite the technical difficulties involved, this procedure may prove of value in the diagnosis of chronic interstitial pancreatitis and other chronic conditions of the pancreas in especially selected cases.

4. Further work is to be done. The attention of other workers is invited.

### REFERENCES

1. Ivy, A. C.: Certain Aspects of the Applied Physiology of External Pancreatic Secretions. *Am. J. Dig. Dis. and Nutrit.*, 9, p. 679, 1936-1937.
2. McCaughan, J. M.: Diagnosis of Pancreatic Disease; Limitations of Present Blood Diastase Test; Suggestion for Increasing Its Effectiveness. *Proc. Soc. Exp. Biol. and Med.*, 40, pp. 665-666, 1940.
3. Comfort, M. W.: Serum Lipase; Its Diagnostic Value. *Am. J. Dig. Dis. and Nutrit.*, 3, pp. 817-821, 1936-1937.
4. Comfort, M. W.: Tests of Pancreatic Function. *J. A. M. A.*, 115, pp. 2044-2050, Dec. 14, 1940.
5. Ivy, A. C.: *Ibid* No. 1, p. 680.
6. McCaughan, J. M.: *Ibid* No. 2, pp. 665-666.

## Pancreatitis in Acute and Chronic Alcoholism\*

By

EUGENE CLARK, M.D.  
NEW YORK, NEW YORK

**A**LTHOUGH there has been some recognition that alcoholism is a predisposing factor in acute and chronic pancreatitis (1-9), the dramatic causal relationship between a prolonged bout of heavy drinking and hemorrhagic pancreatitis is still not generally appreciated, and indeed, the role of alcoholism has been completely ignored in most recent reports on this subject. In the autopsy material which represents the source of this study, and which is distinguished by a high incidence of acute and chronic alcoholism, the role of prolonged alcoholic debauch in the pathogenesis of pancreatitis appears of striking importance, overshadowing, by far, that of chronic gall bladder disease.

The following represents a study of 36 cases of pancreatic disease in alcoholics autopsied during a five year period in the laboratories of Bellevue Hospital and the Office of the Chief Medical Examiner. During this same period, 8 additional instances of alcoholism, with hemorrhagic pancreatitis of such magnitude as to have been held responsible for death, were encount-

ered, but are not included in this report because microscopic studies were not carried out.

Disease of the gall bladder or biliary passages was uniformly absent. In the appended chart are recorded the important findings. In most instances from 10 to 40 blocks were taken from various portions of the pancreas for microscopic study.

Most of the cases occurred during the fourth or fifth decades of life. There were 10 females and 26 males. In 15 instances death was attributable to acute pancreatitis; in 11 the cause of death was cirrhosis of the liver; in 8 "acute and chronic alcoholism" or "alcoholic encephalopathy," and in 2 others death was due to trauma.

### CLINICAL PICTURE

In several instances the patient, when first seen, showed evidence of acute alcoholism, vomited frequently, and complained of pain in the epigastrium, sometimes radiating to the back. The abdomen was generally relaxed but tender; occasionally it was rigid. Signs of shock and leucocytosis were present but glycosuria was not found. Blood amylase studies were not done.

\*From the Department of Pathology of Bellevue Hospital and the New York University College of Medicine and the Office of the Chief Medical Examiner, New York City.  
Submitted Aug. 7, 1942.

Other cases were in alcoholic coma and no history was elicited from the patient. In 2 instances the subject was found dead in bed with empty whiskey bottles at the bedside. In cases 16-26 there was no clinical evidence of the pancreatic lesion. Antemortem diagnosis of hemorrhagic pancreatitis was correctly made in but two instances.

### HISTORY OF ALCOHOLISM

A history of continuously heavy and hard drinking for many months or years was available in all cases. In 14 of the 15 instances in which death was attribu-

table to acute pancreatitis, symptoms appeared or death occurred during or shortly following an alcoholic bout. In 7, chemical examination of the brain indicated the presence of alcohol; in the others no chemical examination was made because death occurred more than 24 hours after admission.

### GROSS FINDINGS

The gross picture varied from that of severe alteration, in which the pancreas appeared as a swollen organ infiltrated with fresh and old blood accompanied by local and widely disseminated fat necrosis, to that

TABLE I  
*Pancreatitis in alcoholism*

| No. | Age | Sex | Cause of Death                   | Pancreas    |       |      |           |        |            | Liver  |      |        | Alcohol     |
|-----|-----|-----|----------------------------------|-------------|-------|------|-----------|--------|------------|--------|------|--------|-------------|
|     |     |     |                                  | Ac. Inflam. | Neer. | Hem. | Fat Neer. | Fibro. | Duct Meta. | Weight | Fat  | Cirrh. |             |
| 1   | 30  | F   | Ac. Paner.                       | ++++        | ++++  | +    | +         | —      | —          | 3500   | ++++ | —      | Ac. & chr.  |
| 2   | 46  | F   | Ac. Paner.                       | ++++        | ++++  | ++   | +         | —      | +          | 2580   | ++++ | —      | Ac. & chr.  |
| 3   | 37  | M   | Ac. Paner.                       | ++++        | ++++  | +++  | ++        | +      | —          | 2000   | ++++ | —      | Ac. & chr.  |
| *4  | 37  | M   | Ac. Paner.                       | ++++        | ++++  | ++++ | ++++      | ++     | ++         | 2400   | +++  | —      | Ac. & chr.  |
| †5  | 38  | M   | Ac. Paner.                       | ++++        | ++++  | ++++ | ++++      | +      | —          | 2180   | +++  | —      | Ac. & chr.  |
| 6   | 55  | M   | Ac. Paner.                       | ++++        | ++++  | ++++ | ++++      | —      | —          | 2100   | +++  | +++    | Ac. & chr.  |
| *7  | 38  | F   | Ac. Paner.                       | +++         | +++   | ++   | ++        | ++     | —          | 1630   | +++  | +++    | Ac. & chr.† |
| 8   | 25  | F   | Ac. Paner.                       | ++++        | ++++  | ++   | +++       | +++    | +++        | 2300   | +++  | —      | Ac. & chr.  |
| 9   | 45  | M   | Ac. Paner.                       | +++         | +++   | ++   | +++       | +++    | —          | 1620   | +++  | —      | Ac. & chr.† |
| 10  | 48  | M   | Ac. Paner.                       | ++++        | ++++  | +++  | +++       | +      | —          | Large  | +++  | —      | Ac. & chr.† |
| *11 | 7   | M   | Ac. Paner.                       | +++         | +++   | +    | +         | +      | —          | 2900   | +++  | +      | ? & chr.    |
| 12  | 38  | M   | Ac. Paner.                       | ++++        | +++   | +++  | +++       | +      | —          | 2190   | +++  | —      | Ac. & chr.† |
| 13  | 42  | M   | Ac. Paner.                       | +++         | +++   | ++   | +++       | ++     | —          | 2470   | ++   | —      | Ac. & chr.  |
| 14  | 45  | M   | Ac. Paner.<br>Rupt. gall bladder | +++         | ++    | —    | —         | —      | —          | 2350   | +++  | —      | Ac. & chr.  |
| 15  | 38  | M   | Pneum. & Ac. P.                  | +++         | ++    | ++   | +         | —      | —          | 3000   | +++  | —      | Ac. & chr.  |
| 16  | 51  | M   | Alc. Enceph.                     | ++          | ++    | —    | —         | —      | —          | 1550   | +    | —      | Ac. & chr.  |
| 17  | 45  | M   | Hep. Cirrh.                      | —           | ++    | —    | —         | —      | —          | 2130   | +++  | +++    | Ac. & chr.  |
| 18  | 48  | F   | Hep. Cirrh.                      | +           | +     | —    | ++        | ++     | +++        | 2950   | ++   | +++    | Chr.        |
| 19  | 74  | F   | Hep. Cirrh.                      | +           | —     | —    | ++        | +++    | —          | 620    | —    | ++++   | Chr.        |
| 20  | 69  | M   | Ac. & chr. alc.                  | +           | +++   | +    | —         | —      | —          | 1600   | +++  | —      | Ac. & chr.† |
| 21  | 45  | F   | Hep. Cirrh.                      | +           | +     | —    | —         | +      | —          | 1850   | +++  | +++    | Chr.        |
| 22  | 56  | M   | Hep. Cirrh.                      | +           | +++   | —    | —         | —      | —          | 1350   | ++   | +++    | Chr.        |
| *23 | 60  | M   | Hep. Cirrh.                      | +           | —     | —    | ++        | ++     | —          | 2990   | +++  | ++     | Chr.        |
| †24 | 38  | M   | Skull Fract.                     | +           | +     | +    | ++        | +++    | —          | 3000   | +++  | —      | ? & chr.    |
| 25  | 39  | M   | Hep. Cirrh.                      | —           | +     | —    | ++        | —      | —          | 2520   | +++  | +++    | Ac. & chr.  |
| 26  | 62  | M   | Hep. Cirrh.                      | —           | —     | —    | +         | +      | —          | 3470   | +++  | +++    | Chr.        |
| 27  | 53  | M   | Alc. Enceph.                     | —           | +     | —    | +         | +      | —          | 2050   | +++  | +      | Chr.        |
| 28  | 26  | F   | Hep. Cirrh.                      | —           | —     | —    | ++        | —      | —          | 2500   | +++  | +++    | Chr.        |
| 29  | 50  | M   | Alc. Enceph.                     | —           | —     | —    | +         | —      | —          | 1600   | +++  | —      | Chr.        |
| 30  | 62  | M   | Hep. Cirrh.                      | —           | —     | —    | +         | +      | —          | 1770   | ++   | +++    | Chr.        |
| 31  | 47  | M   | Hep. Cirrh.                      | —           | —     | —    | ++        | +++    | —          | 4000   | +++  | ++     | Chr.        |
| 32  | 30  | F   | Alc. Enceph.                     | —           | —     | —    | —         | +++    | —          | 2940   | +++  | ++     | Chr.        |
| 33  | 30  | F   | Alc.                             | —           | —     | —    | —         | +++    | —          | 2350   | +++  | —      | Ac. & chr.† |
| 34  | 66  | M   | Mult. Fractures                  | —           | —     | —    | —         | ++     | —          | 2000   | +++  | —      | Ac. & chr.  |
| 35  | 7   | M   | Ac. & chr. alc.                  | —           | —     | —    | +++       | ++     | —          | Large  | +++  | —      | Ac. & chr.  |
| 36  | 42  | M   | Ac. & chr. alc.                  | —           | —     | —    | ++        | ++     | —          | 2400   | +++  | +      | Ac. & chr.† |

\*Ducts open independently.

†Ducts have common opening.

‡Alcohol in brain.





Fig. 1. Photomicrograph of section through one of the smaller pancreatic ducts showing metaplasia of the lining epithelium.

in which only a few foci of fat necrosis or fibrotic changes permitted macroscopic recognition of pancreatic disease.

In 6 instances the duct of Wirsung was opened and traced to its termination; in four (cases 4, 7, 11, 23) the common bile duct and the pancreatic duct had independent openings in the duodenum; in two (cases 5, 24) the ducts possessed a common channel. In the other cases the pancreatic ducts were examined by transverse sections of the organ. In no case was any dilatation of the ducts grossly discernible; the secretion in the duct of Wirsung was colorless and transparent, glary and viscid, and evidence of bile regurgitation was uniformly absent.

#### MICROSCOPIC FINDINGS

By "acute inflammation" is meant the degree of polymorphonuclear leucocytic infiltration. The latter was found in 24 of the cases. Parenchymatous necrosis roughly paralleled acute inflammation. Interstitial hemorrhage occurred in 16 specimens, and in most of these necrosis of the vessel walls was apparent. In 3, terminal thrombosis of the splenic vein was found. Fat necrosis was encountered in 29 cases.

Some degree of fibrosis was present in 24 of the cases. In many it was visible only as small foci in microscopic sections (+), whereas others presented the appearance of a shrunken, densely fibrotic organ (+++).

Fibrotic changes were found in 12 of the 15 cases in which death was attributable to acute pancreatitis. In some instances it was very marked, but distinctly limited to one portion of the pancreas, suggesting previous episodes of pancreatitis which had become spontaneously arrested.

Metaplasia of the pancreatic duct epithelium, as described by Driesel (10) and Baló and Ballón (11) (Plate 1) was marked in two instances (cases 8 and 18), and of lesser degree in 2 others (2 and 4). Much more striking was the presence of deeply eosinophilic inspissated or coagulated secretion within the ducts, either filling them homogeneously or as separated masses (Plate 2). This condition was encountered in

30 of the cases. Dilatation of the smaller ducts was common in areas of fibrosis.

#### ASSOCIATED LIVER DISEASE

In the majority of the cases the liver was considerably enlarged, exceeding 2000 grams in 25 subjects. Cirrhosis was present in 17, and in 3 of these the cirrhotic changes were of such mild character as to be only microscopically visible. In the other 19 cases the liver showed fatty change, generally of very severe degree.

#### DISCUSSION

Of the 36 cases herein described, the predominant morphologic alteration in the pancreas was acute in 19, acute and chronic in 5, chronic in 9, and fat necrosis in 3.

It is not possible to give the exact incidence of this pancreatic disease in alcoholics, but some impression of its frequency may be gained by the occurrence of 27 such cases among approximately 150 consecutive cases of acute and chronic alcoholism seen at necropsy.

These data permit no convincing explanation of the pathogenesis of these lesions. The cases of alcoholism in which the pancreas was normal differed in no significant way from those in which these lesions were found.

The significance of metaplasia of the duct epithelium is not clear. Though it was an impressive finding in some of the cases, its incidence, namely 4 of 36 cases, is no higher than that found by other investigators in the otherwise normal pancreas (7, 10, 11). Rich and Duff (7) were much impressed with this metaplastic duct lesion, and expressed the belief that pancreatitis was initiated by escape of secretion following acinar rupture attributable to obstruction of the smaller pancreatic ducts by the metaplastic epithelium.

It is entirely possible that sharply localized duct alterations of this character, in an organ as large as the pancreas, might be missed in a limited microscopic study. It is also possible that such lesions, when focal, may escape microscopic detection because of destruction by the necrotizing process for which they may be



Fig. 2. Photomicrograph of section through one of the smaller pancreatic ducts showing inspissated coagulum within the lumen.

initially responsible. However, there exists at this time no data which proves a causal relationship between metaplasia of the duct epithelium and pancreatitis, nor is any information available concerning the relative incidence of the former in alcoholics and non-alcoholics.

More frequent and widespread than duct metaplasia was the occurrence of inspissated or coagulated secretion in the pancreatic ducts. Whether this is a cause or the result of the pancreatic lesions, cannot be determined.

There does not appear to be any causal relationship between pancreatitis and cirrhosis of the liver, for the latter has been absent in these cases more often than present. However, the almost constant occurrence of either a large fatty liver or a cirrhotic liver, as well as the uniformity with which a history of prolonged

heavy alcohol indulgence was obtainable, indicate that pancreatitis is more likely to occur in habitual drunkards than in those who only occasionally become intoxicated.

## SUMMARY

Attention is called to the importance of alcoholism in pancreatic disease.

Thirty-six such cases are reported, in whom the pancreatic lesions varied from massive hemorrhagic pancreatitis to alterations of only microscopic dimensions. A fatty or cirrhotic liver accompanied the pancreatic disease, but the gall bladder and biliary passages were normal.

The clinical history or circumstances of death, and the necropsy findings, indicate the causal relationship between habitual drunkenness and pancreatic disease.

## REFERENCES

1. Erdahl, A.: A Review of One Hundred and Five Reported Cases of Acute Pancreatitis, with Special Reference to Etiology. *Bull. Johns Hopkins Hosp.*, 18:130, 1907.
2. Schoel: Quoted by Heiberg, K. A.: Die Krankheiten des Pankreas. J. F. Bergman, 1914, Wiesbaden.
3. Mondon, M. H.: Pancrétite hémorragique. Infarctus mésentérique et Myocardie chez un éthylique. *Soc. méd. hôp., Paris*, 53:542, 1929.
4. Emile, A. and André, J.: Mort subite chez des éthyliques avec pancrétite hémorragique. *Soc. méd. hôp., Paris*, 54:1521, 1930.
5. Gross, O. and Guleke, N.: Die Erkrankungen des Pankreas. Julius Springer, 1924.
6. Myers, W. F. and Keefer, C. S.: Acute Pancreatic Necrosis in Acute and Chronic Alcoholism. *New Eng. J. Med.*, 210:1376, 1934.
7. Rich, A. R. and Duff, G. L.: Experimental and Pathological Studies on the Pathogenesis of Acute Hemorrhagic Pancreatitis. *Bull. Johns Hopkins Hosp.*, 58:137, 1936.
8. Weiner, H. A. and Tennant, R.: A Statistical Study of Acute Hemorrhagic Pancreatitis. *Am. J. Med. Sci.*, 196:167, 1938.
9. Symmers, Wm. St. C.: Acute Alcoholic Pancreatitis. *Dublin J. of Med. Sci.*, 143:244, 1917.
10. Driesel, A.: Beiträge zur Pathologie der Bauchspeicheldrüse. *Frank. Ztschr. f. Path.*, 26:453, 1922.
11. Haló, J. and Ballon, H. C.: Metaplasia of Basal Cells in the Ducts of the Pancreas. *Arch. Path.*, 7:27, 1929.

## Editorials

### AVE ATQUE VALE

THE American Gastro-Enterological Association desired to publish and possess a Journal of their own, and have officially withdrawn as a group from the American Journal of Digestive Diseases. This Journal wishes the Association every success in their new venture (Journal of Gastro-Enterology; Williams and Wilkins, \$6.00 per volume). As individuals, the members of the Association assure us of continued active interest in this Journal. Likewise, the members of the Editorial Council of this Journal will be happy to do all they can to assist the Association editorially or otherwise from time to time. The American Journal of Digestive Diseases becomes with this issue an independent publication devoted to gastro-enterology and nutrition.

From the professional angle, and in view of the long association of this Journal with America's oldest society in this specialty, there are regrets on our part that this separation had to occur. Since we are all physicians united, in any case, by the desire to further the interests of American gastro-enterology, there must remain this valuable bond, which is of greater importance than business considerations. The writer, who has been responsible in the past eight years for piloting this publication through a financial depression, expresses his gratitude to the American Gastro-Enterological Association for their having made this Journal their official publication during most of that period. The relationship was always one of cooperation.

There probably is room in America for at least two good journals of gastro-enterology, and perhaps even the three that soon will exist. In all events, our policy remains fundamentally unchanged, except that we will invite more papers dealing with nutrition and

hormonal metabolism. Some have felt that while the papers we have published were beyond reproach, that possibly too much space has been given to experimental physiology and not enough to snappy clinical articles, and that there should not be any hard and fast line drawn between gastro-enterology and nutrition. With these ideas the writer is in accord, but yet the door never will be closed on good papers dealing with experimental physiology.

The American Journal of Digestive Diseases does not anticipate difficulty obtaining meritorious contributions from clinicians and academic students, because such contributions have already been promised. Furthermore, many members of the Gastro-Enterological Association likewise intend to use the pages of this Journal for publication of some of their articles and this is only a natural attitude, because of the fact that this Journal is long established and enjoys an enviable reader audience.

As an internist, the writer has, for years, devoted special attention to gastro-enterology in most of its phases, and does not feel utterly unqualified for the task of Editor which he now assumes, and he does so strengthened by the assurance of some good old friends that he will not lack for counsel where it is needed.

The invitation is extended to all medical writers and physicians to use this Journal not only as a help in their reading, but as a medium for publication of their ideas about digestive diseases and the many aspects of what we call "nutrition." Papers submitted will receive immediate attention, careful examination, and when accepted for publication, will be printed without undue delay. They will be examined by a group of experienced gastro-enterologists, and suggestions

sometimes will be offered to make acceptable those papers which need re-writing, or which may contain merely a phrase or an expression of an idea which seems to be in battle with accepted gastro-enterological truth. The criterion for rejection is not the presence of iconoclasm, but the degree to which the author has proved the validity of his contention.

There is no doubt that there is considerable satisfaction in reading, or in writing for, a Journal which can claim, as this Journal now claims, to be really *independent*. This means that our policy is not of necessity limited by any preconceived or formulated assumptions or rules produced by any body of men. Politically, we have no one to satisfy. Financially, we have the problem of making a saleable product. In doing this, we must temper popular medical demand by the restraint born of long association with a specialty which, in its formative years, lent itself all too readily to fadism and unsound doctrine. Nevertheless, the writer would be less than frank if he denied that gastro-enterology tends at times toward an official stagnation, and were it not for the invigoration of such physiologists as Ivy, the clear brain and facile pen of such clinicians as Alvarez, and the original clinical researches of such investigators as Crohn, the entire subject might tend to remain in the doldrums of a not-too-classical *impasse*.

This is not intended as a criticism of the endless and patient research of others, nor of the good quality of the papers which organized gastro-enterology has constantly produced. In no other country under the sun has the mine run of papers been anywhere nearly as good, and in no other nation have so many physicians worked steadfastly in this specialty, with the result that we can claim for America a leading role in international gastro-enterology.

At this time, when the majority of the younger men are serving with the armed forces, and are not in a position to undertake clinical research, the rest of us should make a special effort, in spite of added duties, to keep the spirit of investigation from eclipse. This can be better accomplished if we remind ourselves of a responsibility in the matter, here in America, where, if anywhere, clear thinking and good writing still are possible. By industry we can preserve into the post-war period the advances which American gastro-enterology already has registered. The United States has accepted the gargantuan task of providing the rest of the world with food and other essentials of life at a time when their scarcity elsewhere threatens physical life. So too, it becomes our responsibility to provide this more intellectual commodity of a refined science of gastro-enterology, to the end that all warring nations may later derive the reflex benefit. Gastro-enterology began with William Beaumont, as an American science, and the influence of Americans on its further development will be felt in direct proportion to our present perspicacity, industry and determination to keep it from relapse in spite of the hindrances of the world war.

Having thus expressed our editorial policy, it must be apparent that The American Journal of Digestive Diseases has no axe to grind with anyone. We regret the secession of the Association. We salute them officially, with thanks for past favors and promise them our own cooperation in the over-all task to which all physicians are consciously or unconsciously devoted. In our own way, we hope to make the type of contri-

bution to medicine which only an independent organ can hope to make.  
Beaumont S. Cornell.

### PSYCHOSOMATIC INTERRELATIONSHIPS

IT has been the policy of several large medical institutions in the past decade, to side-step conceptions of psychology which admit the possibility that a mental state can be the cause of a physical ailment. Following the work of Walter B. Cannon, it could no longer be denied that a close relationship existed between the emotions and the production of the internal secretions. The behavior of the adrenals in states of hunger, fear and rage was so scientifically demonstrated, that the most logical mind in medicine was forced to admit that a tangible connection existed between what we term mind and what we term body. The well-written work by Flanders Dunbar, "Emotions and Bodily Changes" (Columbia University) appeared in 1935, and this book still serves as the best reference text for those interested in this vast problem. The scope of this book was extensive and it was no more remarkable for its collection of clinical data than for its natural intrusion into the fields of philosophy related to the main problem of the behavior of the body under influence from the mind.

The universities themselves have taken an attitude of reasonable admission of the proportion that the mind can, and does, produce changes in the physiological reactions of the body, and they have spent time and money, not only on formal psychological and psychiatric investigations, but even on clinico-laboratory tests of the validity of the main thesis. On the other hand, many medical institutions which depend upon popular employment of their services for subsistence and profit, have found it wise to refrain from a too-evident sanction of the idea, largely because the patients resent the inference that they themselves could be held psychologically responsible for the very processes of functional pathology which prompted them to employ the institution.

However, although this pandering to the whim of the public is one of the worldly-wise elements in the restraint of these institutions, it is not the only reason, or even the chief reason, for their attitude. The fact is that many clinicians, dealing daily with problems of organic pathology and disease, have felt that most effort, at this stage of clinical investigation, ought to be expended upon the more tangible aspects of disease, which in themselves present difficulties still unsolved. Many feel that time spent on the study of mental states, emotional "feeling tones" and the "reaction types" of patients is often an ill-advised occupation, especially by physicians who are likely to overlook some recondite physical pathology, elusive to even the best and most scientific methods of examination. What is the sense in determining that an individual is suffering from an involuntal melancholia, when he is also harboring an operable carcinoma of the ascending colon? It is admitted that such clinicians are justified in their cautious attitude. The patient's money and confidence should be rewarded by at least an expert physical diagnosis. Nevertheless, the mental phase of the patient, if it can be ascertained without overlooking a fundamental physical lesion, adds to the accuracy of the estimate of the patient as a whole, and provides a more "inventory" type of diagnosis.

Freud succeeded chiefly in providing medicine with a method of psychic examination of great value, and he would not be partially discounted today, save for the fact that his philosophy of life was too biased to be accepted by persons daily having regard for at least a routine decency of mind. Psychiatric medicine today involves not one, but many ramifications. There are many practitioners, who, using Freud for what he is worth, manage, after much enquiry and suggestion, to arrive at positions which actually do prove of value to the suffering individual. There can scarcely be said to exist any formulation of what is permissible and non-permissible among the ramifying schools of thought in psycho-analytical medicine today, and this lack of formulation is a healthy sign of a growing science. Terminology also suffers from the same lack of definition, so that if a patient is confused, it is all right merely to label the case one of confusion, or if agitated, simply to call it a case of agitation, or if worried, merely to name it worry, or anxiety. While thankful for this admirable simplification, the general profession shows a growing impatience with the Freudian philosophy of life which causes so many analysts still to harp eternally on the sexual problem, with its wearying symbology. It is felt that sometime a balance will be hit upon, and the psychologists will revise their estimates of man, as a psycho-biological creature, and bring forth a philosophy more complimentary to his possible dignity and destiny.

As a practical method of invading this field of the psychosomatic interrelationships, the Society for Research in Psychosomatic Problems\* deserves consideration and support from every physician who feels that the mental element in man must be regarded as an integral part of his total manifestations. Perhaps it is safe to state that any other attitude would be utterly impossible were it not for our inveterate flare for analysis. Even to state that medicine can ever accomplish much by a reverse process of synthesis, is today running the risk of being misunderstood, or of being decidedly premature. Certainly, the day of ultra-analysis is not past, and we shall see much good resulting from such continued method of research. But there can be no harm in having both processes—namely that of analysis and that of synthesis—going on together.

In gastro-enterology, we already have, in some of the large cities, men who are devoting their time to the purely mental aspects of patients suffering from functional disorders of the digestive tract, and while it cannot be said that their work has received any signal recognition, it is nevertheless, true that their work should be better understood, and that psychology, as applied to digestive disorders, should be regarded, not as an unwelcome intrusion, but as a tender subsistence, which some day may prove the value of its tenets.

This Journal, therefore, will welcome contributions which wisely deal with the psychological aspects of gastro-enterology, but will never lend itself to any biased attitude which would over-emphasize the importance of such studies today, when, as everyone knows, we are far from a scientific understanding of the purely physical workings of the human body.

\*The Society for Research in Psychosomatic Problems will meet on December 18, 1942, at 8 p. m. at the Waldorf Astoria Hotel, New York City.

## WILLIAM C. MENNINGER, M.D.

WE welcome to our staff at this time, William C. Menninger of Topeka, Kansas, who becomes the first member of our newly-inaugurated department of Neurology and Psychiatry. Dr. Menninger is well-known as a distinguished neuropsychiatrist and is the author of "Juvenile Paresis." In addition to his clinical appointments, he has found time to express his social consciousness in many welfare undertakings, of which his work with and for, Sea Scouts lies nearest to his heart. It is the long-held opinion of Dr. Menninger that of all phases of medicine, gastro-enterology is the most fertile field in which search may be made for the influence of the psychological factors. His contributions in the future will, we are certain, greatly assist us in our evaluation of the importance of psychosomatic inter-relationships and point up a new angle of study for those interested in not one, but all phases of gastro-enterology.

## THE PHYSICIAN'S ATTITUDE TOWARD VITAMINS

TODAY when vitamins are sold over the counter in chain grocery stores very much as foods are sold, with the public protected by our Federal pure food laws, and with this sale backed up by constant and intensive radio, newspaper and magazine advertising, the physician frequently finds it unnecessary to prescribe these food products, merely because the patient already has been taking them in some sort of combination long before the physician was consulted. It has not been convincingly demonstrated that the use of vitamins in reasonable doses does human beings any harm, even when they are used over prolonged periods. On the contrary, medical observation, if frankly reported, probably would indicate that the habit is good rather than vicious and results in fewer respiratory infections, greater vigor and an increased sense of well-being.

That the most ardent self-medicator with vitamins may, however, become ill demonstrates that the vitamin habit is no proof against disease and ought not to be regarded as the cure-all of the long list of human ailments. The whole indoctrination of the public on the broad subject of nutrition, now being intensified by national and domestic agencies cannot be regarded as, in any sense, ill-advised. The results obviously are good, because the individual not only learns the well-accepted ideas of following a diversified and balanced diet, more or less suited to his age, weight and occupation, but he gains a genuine inspiration from the new ideas opened up for him. The nutrition campaign, now reaching its all-time high in America, may be expected to result, in due course, in a broad improvement in national health, a gradual lowering of industrial time loss, and a better standard of eating. The good accomplished by the establishment of the "milk bars" in England a decade ago, did much, in the opinion of the British Health Ministry, to raise the general state of health of English youth at a time when they presented alarming signs of malnutrition and waning vigor. The extra feedings of school children practiced by many educational aid societies is doing an inestimable amount of good for undernourished and impoverished children. The present educational campaign emanating from our Federal

Government, has given very wide publicity to the necessity of fortifying white flour bread with Vitamin B. This particular campaign will, no doubt, result in more widespread improvement in the general nutrition of the public than any other single vitamin campaign, private or public, to date.

Some forty years ago, when the campaigns against tuberculosis were getting under way, the need of fresh air in the prevention of the disease was recognized, and physicians advised all run-down persons to sleep with their bedroom windows open. Today we seldom make this suggestion because we assume that everyone does so already. Similarly, the novelty phase of vitamin treatment may be said to have ended, and the time is almost at hand when we shall be assuming that the patient is naturally wise enough to see to it that he receives sufficient vitamins of all known kinds for his daily needs. Having finally been persuaded that this is the case, we shall largely discount the effects of vitamin deprivation in dealing with any given diagnostic or therapeutic problem. It is unnecessary to state that this time has not as yet arrived, and we must still keep in mind the possibility of borderline cases of vitamin deprivation, and make sure on general principles that the patient is receiving sufficient amounts.

The more expert we become in prescribing diets for sick persons, the greater is our tendency to depart as little as possible from the so-called "normal" or "average" diet, because we have learned from experience that most patients get better faster on such a diet than on those bizarre dietary abstractions which still are handed to patients for no decipherable reason. It goes without saying that special diets are essential in diabetes, advanced nephritis, adiposity, hypertrophic arthritis and certain other diseases, but even in these, the trend is away from the severe caloric and protein deprivation, practiced in the past decade. While we have thus found that it is not always good to take away foods, it is frequently advisable to add special supplements. Today, almost all physicians are

alive to the admitted necessity of providing adequate vitamin protection in the diets of all types of patients and diseases. Numerous instances of "miraculous" improvements undoubtedly are found under circumstances where the diet previously was lacking in the important food elements here under discussion. On the other hand, we ought to remember that when, as so often happens, we can see no benefit from vitamin therapy, the failure is due to giving the patient something of which he already has enough. The public have been unduly agitated by the general advertising of vitamins, and the average physician is irked by their reflex anxiety in the matter, as shown by the questions of his patients. A balance soon will be struck. Vitamins will be clinically assessed for their full value in disease and health. It will be realized that vitamin deprivation is not the one, and only, cause of disease. It will be later assumed that the patient has taken care of his own vitamin needs in advance, and this assumption, while often erroneous, will permit us to become conscious of other aspects of the case. Already, the aggregate of opinion among medical men is that too much was at first expected of dietary supplements. Perhaps less has been accomplished clinically than had been expected. There is no evidence that life has been prolonged by vitamin therapy. The role of vitamins in increasing resistance to infection, while real, is nevertheless by no means a fool-proof insurance. Except in clear cut cases of avitaminosis of specific type, it may be said that vitamin therapy, while of great value in improving the health of the public, has been less effective and dramatic than chemotherapy and hormone therapy in the actual clinical battle against disease and death.

#### ERROR

"The article by B. Slutzky and N. Dietz in the October issue was inadvertently titled "The Effect of Histamine on Cinchophen Ulcers Produced in Dogs," whereas the title should have been "The Effect of Histaminase on Cinchophen Ulcers Produced in Dogs."

## Abstracts of Current Literature

FRANKLIN HOLLANDER, Associate Editor in Charge of Abstracts, New York, N. Y.

ALBERT CORNELL, New York, N. Y.  
MAURICE FELDMAN, Baltimore, Md.  
CHARLES A. FLOOD, New York, N. Y.  
M. H. F. FRIEDMAN, Philadelphia, Pa.  
J. DUFFY HANCOCK, Louisville, Ky.  
THOMAS A. JOHNSON, Philadelphia, Pa.  
ALLEN A. JONES, Buffalo, N. Y.  
N. W. JONES, Portland, Ore.  
HENRY H. LERNER, Boston, Mass.  
PHILLIP LEVITSKY, Montreal, Can.

JESSIE LOVE, Louisville, Ky.  
FRANZ J. LUST, New York, N. Y.  
IRA A. MANVILLE, Portland, Ore.  
ARTHUR E. MEYER, Brooklyn, N. Y.  
FRANCIS MURPHY, Milwaukee, Wis.  
H. NECUELES, Chicago, Ill.  
FRANK NEUWELT, Gary, Indiana  
SAM OVERSTREET, Louisville, Ky.  
J. F. PESSER, Trenton, N. J.  
DAVID J. SANDWEISS, Detroit, Mich.

RUDOLF SCHINDLER, Chicago, Ill.  
MICHAEL SHUTKIN, Milwaukee, Wis.  
VIRGIL E. SIMPSON, Louisville, Ky.  
H. J. SIMS, Denver, Colo.  
HENRY TUMEN, Philadelphia, Pa.  
ROBERT TURELL, New York, N. Y.  
EDGAR WAYBURN, San Francisco, Calif.  
JOHN WILLARD, Philadelphia, Pa.  
C. WILMER WIRTS, Philadelphia, Pa.

[Microfilm copies of papers may be obtained from Microfilm Service of the Army Medical Library at 25c for each complete article, not exceeding 25 pages in length—and 10c for each additional 10 pages or fraction thereof. Prepayment is not requested. Remittance may be made with subsequent orders and in such manner as found most convenient. Address—Microfilm Service, Army Medical Library, Washington, D. C.]

#### CLINICAL MEDICINE MOUTH AND ESOPHAGUS

WALLACE, R. P.: *Traction Diverticulum of the Esophagus*. *Med. Clinics N. Am.*, 26:889, May, 1942.

Wallace takes forty cases of traction diverticulum of the esophagus. Symptoms were directly due to the diverticulum in 38.5 per cent, and in most instances constituted the chief complaint. For the most part the symptoms were mild and consisted of pain behind the sternum, burning or a sensation of heaviness. Usually the pain was referred to the midsternal region, but when severe was not localized. There was no constant radiation of the pain. Dysphagia was a common symptom, and swallowing was not only painful but difficult. Gross hemorrhage from the

diverticulum, with or without melena, occurred in three cases, the remainder of the upper gastro-intestinal tract being free from disease.

The author emphasizes the importance of a proper contrast medium. He prefers a freshly prepared barium and mucilage of acaëia mixture.

The treatment of this condition is very unsatisfactory. Surgery is hardly ever used. A smooth diet is recommended. Lubricants are prescribed as petrolatum and olive oil. Besides sedatives and antispasmodics are used in full dosage up to the point of tolerance. Occasionally dilatation of the esophagus has been followed by some relief of symptoms.—Franz Lust.

*American Journal of*  
DIGESTIVE DISEASES  
Volume 9



# Author Index for Volume Nine

|                          |                             |                              |               |
|--------------------------|-----------------------------|------------------------------|---------------|
| Abbott, W. Osler         | 202                         | Gatewood, L. C.              | 359           |
| Aggeler, P. M.           | 227                         | Gershon-Cohen, J.            | 124, 363      |
| Alvarez, Walter C.       | 47, 113, 114, 209, 239, 357 | Ginzburg, Leon               | 64            |
| Andresen, Albert F. R.   | 91                          | Goldstein, Hyman I.          | 85            |
| Andrews, Katherine       | 109                         | Golob, Meyer                 | 120           |
| Antopol, William         | 342                         | Goodman, Jerome E.           | 399           |
| Asher, Leonard           | 109                         | Gordon, George B.            | 397           |
|                          |                             | Gross, E. G.                 | 234           |
| Baker, Charles Frederick | 76                          |                              |               |
| Baltz, James I.          | 13                          | Hall, Augustus A.            | 389           |
| Banks, B. M.             | 350                         | Hardt, Leo L.                | 404           |
| Barborka, Clifford J.    | 309                         | Harris, Seale                | 29            |
| Bargen, J. Arnold        | 147                         | Harris, Seale, Jr.           | 29            |
| Bauer, Richard           | 387                         | Hasterlik, Robert J.         | 49, 78, 183   |
| Beazell, J. M.           | 82                          | Helm, John D.                | 141           |
| Beling, C. Abbott        | 76                          | Heyd, Charles Gordon         | 348           |
| Berardi, J. B.           | 292                         | Hinnink, J. W. G. ten Bokkel | 168           |
| Bercovitz, Z.            | 327, 419                    | Hinton, J. William           | 317           |
| Bergh, George S.         | 40, 162                     | Hirschberg, Nell             | 200           |
| Berk, J. Edward          | 106, 276, 297, 371          | Hoelzel, Frederick           | 188           |
| Berman, A. L.            | 82                          | Holder, Ernest C.            | 237           |
| Blick, Philip            | 292                         | Hollander, Franklin          | 332           |
| Boles, Russell S.        | 241                         | Hollands, Robert A.          | 13            |
| Brewer, W. A.            | 68                          | Hough, V. H.                 | 82            |
| Brittain, Knox           | 307                         |                              |               |
| Brown, Philip W.         | 87                          | Ingram, W. R.                | 234           |
| Browne, Donovan C.       | 177, 407                    | Ivy, A. C.                   | 82            |
| Bullock, Jesse G. M.     | 237                         |                              |               |
|                          |                             | Jackman, Raymond J.          | 147, 220      |
| Cantarow, A.             | 101                         | Jacobi, Mendel               | 264           |
| Castigliano, S. G.       | 425                         | Jankelson, I. R.             | 99            |
| Chaikin, N. W.           | 150                         | Jones, Charles A.            | 1             |
| Chamberlin, Donald T.    | 245                         |                              |               |
| Chornock, Francis W.     | 74                          | Kantor, John L.              | 120           |
| Church, Reynold E.       | 317                         | Kirklin, B. R.               | 313           |
| Clark, Eugene            | 428                         | Kirschen, M.                 | 154           |
| Clark, George E., Jr.    | 401                         | Kirsner, Joseph B.           | 229           |
| Clendening, Logan        | 188                         | Klein, Bernard               | 264           |
| Colp, Ralph              | 64                          | Kogut, Benjamin              | 264           |
| Cooper, Ralph R.         | 395                         | Kozoll, D. D.                | 36            |
| Cornell, Albert          | 332                         | Kraemer, Manfred             | 129, 338, 356 |
| Coulter, John S.         | 404                         |                              |               |
| Craver, Bradford N.      | 223                         | Large, A. M.                 | 303           |
| Crohn, Burrill B.        | 79, 358                     | Laufman, Harold              | 144           |
|                          |                             | Layne, John A.               | 162           |
| Davenport, Horace W.     | 416                         | Lerner, Henry H.             | 109           |
| De Carvajal-Forero, Jose | 268                         | Leser, Ralph U.              | 78            |
| Diamond, Mortimer        | 144                         | Levine, Samuel               | 397           |
| Dickey, Francis G.       | 74                          | Levy, Jerome S.              | 198, 354      |
| Dietz, N.                | 352                         | Levy, Joseph G.              | 237           |
| Donald, Charles J., Jr.  | 87                          | Lucia, S. P.                 | 227           |
| Drosd, Rudolph           | 79                          | Lusk, Harry                  | 395           |
| Druckerman, Leonard J.   | 282                         |                              |               |
|                          |                             | Machella, Thomas E.          | 141           |
| Einsel, I. H.            | 191                         | Marion, Donald F.            | 13            |
| Elman, R.                | 303                         | Marlett, N. C.               | 329           |
| Elsom, Kendall A.        | 74                          | Marquis, W. James            | 76            |
| Emery, Edward S., Jr.    | 281                         | Martin, Gustav J.            | 268           |
| Eusterman, George B.     | 301, 313                    | Mateer, John G.              | 13            |
|                          |                             | McCausland, Alexander        | 329           |
| Feldman, Maurice         | 195, 211, 399               | McGann, R. J.                | 55            |
| Fels, Samuel S.          | 124, 363                    | McGee, Lemuel C.             | 329           |
| Fishbon, H. M.           | 227                         | McGlade, H. B.               | 137           |
| Fleming, Ralph G.        | 115                         | McHardy, Gordon              | 177, 407      |
| Fogelson, Samuel J.      | 173                         | McIver, Monroe A.            | 52            |
| Folley, Jarrett H.       | 202                         | Meyer, Jacob                 | 157, 160      |
| Forsythe, John R.        | 401                         | Miller, Joseph M.            | 383           |
| Friedenwald, Julius      | 273                         | Miller, Lila                 | 68            |
| Friedman, M. H. F.       | 166, 275                    | Mintz, I. Lew                | 289           |
| Fugo, N. W.              | 234                         | Moersch, Herman J.           | 287           |
|                          |                             | Morlock, Carl G.             | 313           |
| Garlock, John            | 64                          | Moser, Rollin H.             | 49, 183       |
| Garner, Jay M.           | 140                         | Moss, Harold K.              | 110           |

|                                  |                        |                                 |                    |
|----------------------------------|------------------------|---------------------------------|--------------------|
| Neecheles, H. . . . .            | 36, 151, 154, 157, 160 | Shwartzman, Gregory . . . . .   | 133                |
| Nesselrod, J. F. . . . .         | 140                    | Siler, Kenneth A. . . . .       | 354                |
| Newman, Bernard . . . . .        | 43                     | Siplet, Herman . . . . .        | 363                |
| Olleros, A. Rodriguez . . . . .  | 261                    | Slutzky, B. . . . .             | 352                |
| Ortmayer, Marie . . . . .        | 411                    | Smith, Lucian A. . . . .        | 301                |
| Page, Robert C. . . . .          | 419                    | Smith, Newton D. . . . .        | 181                |
| Palmer, Walter Lincoln . . . . . | 229                    | Smith, Randolph T. . . . .      | 198                |
| Patterson, Thomas L. . . . .     | 375                    | Smith, William M. . . . .       | 340                |
| Pelner, Louis . . . . .          | 417                    | Snell, Albert M. . . . .        | 115                |
| Penner, Abraham . . . . .        | 282                    | Sorter, H. . . . .              | 154, 160           |
| Pessel, J. F. . . . .            | 140                    | Steigmann, F. . . . .           | 423                |
| Plötke, F. . . . .               | 157                    | Stein, Justin J. . . . .        | 192                |
| Plume, C. A. . . . .             | 329                    | Stevens, Richard J. . . . .     | 110                |
| Pollard, H. M. . . . .           | 68                     | Svien, Hendrik J. . . . .       | 45                 |
| Popper, H. L. . . . .            | 186                    | Tannenbaum, Oscar . . . . .     | 150                |
| Rafsky, Henry A. . . . .         | 43                     | Thomas, J. Earl . . . . .       | 106, 276, 297, 371 |
| Reh fuss, Martin E. . . . .      | 106, 276, 297, 371     | Thompson, Marvin R. . . . .     | 268                |
| Reich, Frederick . . . . .       | 98                     | Tuchman, Lester . . . . .       | 342                |
| Reingold, I. . . . .             | 151                    | Turell, Robert . . . . .        | 248                |
| Renshaw, John F. . . . .         | 401                    | Val Dez, Frank C. . . . .       | 367                |
| Rivers, Andrew B. . . . .        | 45                     | Wakefield, E. G. . . . .        | 181, 383           |
| Rodaniche, Enid C. . . . .       | 229                    | Walker, Burnham S. . . . .      | 223                |
| Rosenak, Bernard D. . . . .      | 49, 183                | Warren, Althea A. . . . .       | 205                |
| Sagall, E. . . . .               | 350                    | Wayburn, Edgar . . . . .        | 392                |
| Sailer, Seaton . . . . .         | 55                     | Weber, C. J. . . . .            | 188                |
| Sandweiss, David J. . . . .      | 166, 289, 375          | Weil, Lester . . . . .          | 264                |
| Schiff, Leon . . . . .           | 110                    | Weinberg, Tobias . . . . .      | 399                |
| Schiff rin, M. J. . . . .        | 205                    | Weir, James F. . . . .          | 287                |
| Schiff rin, Arthur . . . . .     | 342                    | Weisel, Wilson . . . . .        | 181                |
| Schindler, Rudolf . . . . .      | 149, 289, 340, 411     | Weissman, Morris . . . . .      | 404                |
| Sch nedorf, J. G. . . . .        | 188                    | Wilcn, Carl . . . . .           | 407                |
| Schwartz, A. . . . .             | 151                    | Wilkinson, S. Allen . . . . .   | 321                |
| Sendroy, Julius, Jr. . . . .     | 367                    | Winkelstein, Asher . . . . .    | 133, 332           |
| Serby, A. M. . . . .             | 98                     | Wirts, C. W., Jr. . . . .       | 101                |
| Shay, Harry . . . . .            | 124, 363               | Wozasek, Oskar . . . . .        | 292, 423           |
| Sheehan, Donal . . . . .         | 361                    | Zetzel, I. . . . .              | 350                |
| Shoch, David . . . . .           | 173                    | Zuckerman, I. Charles . . . . . | 264                |

## General Index for Volume Nine

|                                     |               |  |             |
|-------------------------------------|---------------|--|-------------|
| Abdominal wall . . . . .            | 392           | Alkalosis . . . . .                      | 322         |
| Abnormalities of appendix . . . . . | 215           | Allergy, in ulcerative colitis . . . . . | 91          |
| Abscess, perirectal . . . . .       | 181           | test diet . . . . .                      | 95          |
| Absorption of amino-acid . . . . .  | 350           | Alternaria . . . . .                     | 201         |
| Accessory pancreas . . . . .        | 217           | Aluminum hydroxide . . . . .             | 332, 335    |
| Acetarsone . . . . .                | 360           | phosphate . . . . .                      | 336         |
| Acetobacter . . . . .               | 200           | phosphate gels . . . . .                 | 332         |
| Acetysulfanilamide . . . . .        | 416           | Amebiasis . . . . .                      | 360         |
| Achlorhydria . . . . .              | 212, 261, 314 | Amebic dysentery . . . . .               | 253         |
| Achylia . . . . .                   | 212           | Amino acids . . . . .                    | 173, 354    |
| Acid factor . . . . .               | 371           | Amino-acid absorption . . . . .          | 350         |
| secretion . . . . .                 | 416           | Amniotic fluid . . . . .                 | 275         |
| Acidity, gastric . . . . .          | 332           | Amoebic dysentery . . . . .              | 247, 328    |
| Actinomyces . . . . .               | 201           | Amorphous secretin . . . . .             | 68          |
| Actinomycosis . . . . .             | 254, 418      | Amylase . . . . .                        | 69, 70      |
| Acute gastro-enteritis . . . . .    | 247           | Amyl nitrite . . . . .                   | 37          |
| pancreatitis . . . . .              | 186, 305      | Anacidity . . . . .                      | 340         |
| Adenoma . . . . .                   | 216           | Anal incontinence . . . . .              | 256         |
| benign . . . . .                    | 149           | Analysis, lipolytic . . . . .            | 223         |
| Adhesions . . . . .                 | 316           | Anastomotic ulcer . . . . .              | 313         |
| Adrenalin . . . . .                 | 36            | Anemia . . . . .                         | 65, 87, 330 |
| African sleeping sickness . . . . . | 329           | pernicious . . . . .                     | 261         |
| Air in biliary tract . . . . .      | 215           | Anomalics of midgut . . . . .            | 383         |
| Alcohol . . . . .                   | 331           | Anorectal gonorrhea . . . . .            | 255         |
| influence on colon . . . . .        | 258           | infections . . . . .                     | 144         |
| Alcoholic beverages . . . . .       | 115           | lesions . . . . .                        | 258         |
| intoxication . . . . .              | 82            | Anorectum . . . . .                      | 248         |
| pellagra . . . . .                  | 35            | Anorexia nervosa . . . . .               | 227         |
| Alcoholism . . . . .                | 428           | Antacids . . . . .                       | 375         |
|                                     |               | Anti-spasmodics . . . . .                | 319         |

|                               |                    |  |                        |
|-------------------------------|--------------------|--|------------------------|
| Antitoxic B. coli serum       | 133                | of colon                               | 215, 251               |
| Army diagnostic key           | 391                | of common duct                         | 343                    |
| Army, ulcer and colon in      | 245                | of liver                               | 217                    |
| Arsenic poisoning             | 360                | of pancreas                            | 68, 113, 217, 304      |
| Artificial gastric juice      | 209                | of stomach                             | 79, 247, 287           |
| Ascites                       | 62, 115            | Cardiospasm                            | 247                    |
| Ascorbic acid                 | 191                | Carmine                                | 154                    |
| Aspergillus                   | 201                | Carrots                                | 189                    |
| Asynergia                     | 358                | Casein                                 | 175, 351               |
| Atabrine                      | 327                | digest                                 | 354                    |
| Atresia of esophagus          | 211                | Catalysts                              | 309                    |
| Atrophic gastritis            | 78, 149, 262, 341  | Catarrhal jaundice                     | 247                    |
| Atrophy, gastric              | 404                | Cecal volvulus                         | 177                    |
| of gastric mucosa             | 98                 | Cecocolon                              | 177                    |
| of liver                      | 1                  | Cellulase                              | 200                    |
| Atropine                      | 202, 211, 293      | Cellulose                              | 387                    |
| Autolysis                     | 406                | splitting micro-organisms              | 200                    |
| Avitaminosis A                | 74                 | Cephalin-cholesterol flocculation test | 13                     |
| Azotemia                      | 110                | Cheilosis                              | 191, 350               |
| Bacillary dysentery           | 247, 252, 328, 359 | Child with ulcer                       | 338                    |
| Bacteria, cellulose-splitting | 200                | Chiniofon                              | 328, 360               |
| Bad taste                     | 81                 | Cholangiograms                         | 306                    |
| Balantidium coli              | 360                | Cholangiography                        | 216                    |
| Banti's disease               | 115                | Cholecystectomy                        | 49                     |
| Barium chloride               | 294                | Cholecystitis                          | 100                    |
| B. coli serum                 | 133                | Cholecystography                       | 216                    |
| B. complex deficiencies       | 268                | Cholecystokinin                        | 68                     |
| Belching                      | 49                 | Cholelithiasis                         | 100, 247               |
| Belladonna                    | 36                 | Cholemic death                         | 348                    |
| Benign adenomas               | 149                | Cholesterol                            | 264                    |
| Benzedrine                    | 202                | in blood                               | 1                      |
| Benzidine test                | 154                | Cholic acid                            | 82                     |
| Bicarbonate                   | 68                 | Choline                                | 268                    |
| Bile pigments                 | 69, 168            | Cholinesterase                         | 342                    |
| Bile salts                    | 51                 | Chromoscopy                            | 263                    |
| Biliary duct, obstruction of  | 1                  | Chronic amoebiasis                     | 328                    |
| dyskinesia                    | 51                 | constipation                           | 257                    |
| obstruction                   | 397                | gastric ulcer                          | 338                    |
| physiology                    | 264                | gastritis                              | 86, 411                |
| Blacktongue                   | 118                | ulcerative colitis                     | 147, 251               |
| Bleeding from rectum          | 258                | Chyladenectasia                        | 57                     |
| gums                          | 189                | Chylomicrons                           | 395                    |
| peptic ulcer                  | 150                | Cinchophen ulcers                      | 352                    |
| Bloating                      | 49                 | Cinematography, proctoscopic           | 140                    |
| Blood cholesterol             | 1                  | Cirrhosis                              | 5                      |
| enzymes                       | 160                | of liver                               | 35, 100, 247, 342, 392 |
| occult                        | 154                | Citrus fruits                          | 189                    |
| sugar                         | 151                | Clotting time                          | 420                    |
| urea nitrogen                 | 110                | Coagulation of serum                   | 129                    |
| Boils                         | 189                | Coated tongue                          | 81                     |
| Bowel and hypothalamus        | 361                | Codeine phosphate                      | 37                     |
| Bread                         | 189                | Cod liver oil                          | 268                    |
| Brewers' yeast                | 119                | Cold abscess                           | 409                    |
| Bromoform manometer           | 380                | allergy                                | 352                    |
| Bromsulphthalein excretion    | 101                | Colitis, thrombo-ulcerative            | 147                    |
| test                          | 141                | ulcerative                             | 133, 229, 356, 419     |
| Butter fat                    | 268                | Colloidal antacids                     | 332                    |
| Cachexia                      | 160                | gold test                              | 13                     |
| Calcifications                | 217                | kaolin                                 | 213                    |
| Calcium                       | 367                | Colon                                  | 248                    |
| chloride                      | 129                | bacilli                                | 356                    |
| pantothenate                  | 268                | irritable                              | 245, 281               |
| Calculus, parotid duct        | 417                | irritation                             | 423                    |
| Campolom                      | 119                | Colonic allergy                        | 258                    |
| Cancer                        | 409                | cancer                                 | 210                    |
| of colon                      | 307                | flatul                                 | 258                    |
| of gall bladder               | 343                | Color indicators                       | 106                    |
| of head of pancreas           | 217                | Coma                                   | 348                    |
| of stomach                    | 239                | Common duct stones                     | 52                     |
| Carbarsone                    | 360                | Congenital obstruction                 | 214                    |
| Carcinoid tumors              | 215                | umbilical hernia                       | 383                    |
| Carcinoma                     | 112, 195, 213      | Conjunctivitis                         | 191                    |
| of ampulla of Vater           | 216                | Control, of acid                       | 124                    |
| of anus                       | 249                | Corn                                   | 189                    |
| of cardia                     | 86                 | Cyanosis                               | 330                    |

|  |                              |                            |                              |
|--|------------------------------|----------------------------|------------------------------|
| Cyst, mucosal                          | 399                          | Famine                     | 309                          |
| Cyverine                               | 37                           | Fatigue                    | 151                          |
| Decomposition of cellulose             | 200                          | Fatty acids                | 264                          |
| Deficiency disease                     | 309                          | liver                      | 303                          |
| states                                 | 253                          | Fear                       | 188                          |
| Deglutition                            | 285                          | Fecal vomiting             | 193                          |
| Depressant, gastric secretory          | 166                          | Feces, bulk of             | 423                          |
| Diabetes mellitus                      | 363                          | Feculent eructation        | 193                          |
| Diarrhea                               | 57, 87, 189, 193, 261, 360   | Fever, indeterminate       | 181                          |
| post-operative                         | 90                           | Fibrinogen                 | 419                          |
| Diastase, serum                        | 425                          | Fibrous fruits             | 200                          |
| Diet-cellulose                         | 387                          | Fistula                    | 87                           |
| Diets, amino-acid                      | 173                          | duodeno-colic              | 195                          |
| Dimethylaminoazobenzene                | 109                          | gastrojejuno-colic         | 192, 195                     |
| Dinitrotoluene                         | 329                          | Fistulae                   | 215                          |
| Diodoquin                              | 328, 360                     | Flatulence                 | 405                          |
| Disease, tropical                      | 327                          | Folliculitis               | 189                          |
| Disorders, intestinal                  | 359                          | Food                       | 40                           |
| Disseminated calcification of pancreas | 76                           | Food production            | 310                          |
| Disturbances, metabolic                | 329                          | Foreign bodies             | 256                          |
| Diverticula of duodenum                | 398                          | Free acidity               | 354                          |
| of stomach                             | 212                          | Fructose tolerance test    | 82                           |
| Diverticulitis                         | 251                          | Fungi                      | 200                          |
| of sigmoid                             | 247                          | Galactose                  | 343                          |
| Diverticulosis                         | 215, 251                     | Gall bladder, double       | 120                          |
| Dizziness                              | 151, 330                     | dyspepsia                  | 49                           |
| Dogs, Mann-Williamson                  | 173                          | varices of                 | 399                          |
| Double cystic duct                     | 216                          | Gall stone                 | 215                          |
| Double gall bladder                    | 120                          | Gangrene of foot           | 301                          |
| Dreaming                               | 137                          | Garlic                     | 80                           |
| Drip method                            | 332                          | Gas                        | 49                           |
| Duodenal acidity                       | 371                          | Gastric acid               | 124                          |
| bulb                                   | 371                          | acidity                    | 188, 332, 354, 367           |
| contents                               | 223                          | anacidity                  | 363                          |
| diverticula                            | 213                          | analysis                   | 106                          |
| fistulas                               | 371                          | atrophy                    | 404                          |
| instillation                           | 354                          | carcinoma                  | 79, 340                      |
| juice                                  | 98                           | dilatation                 | 348                          |
| obstruction                            | 45                           | emptying                   | 202, 315                     |
| papilla                                | 213                          | hypersecretion             | 297                          |
| ulcer                                  | 124, 358, 371, 375, 377, 397 | juice                      | 206                          |
| Duodeno-colic fistula                  | 195                          | motility                   | 137, 375                     |
| Duodenum, neutralizing ability         | 297                          | motor function             | 315                          |
| Dysentery bacteriophage                | 328                          | mucosa                     | 109, 149, 407                |
| Dyspepsia, due to gall bladder         | 49                           | mucosa redundant           | 287                          |
| Dysphagia                              | 211, 282                     | obstruction                | 315                          |
|  |                              | retention                  | 212, 316                     |
|  |                              | secretion                  | 234, 363, 416                |
|  |                              | in newborn                 | 275                          |
|  |                              | secretory depressant       | 166                          |
|  |                              | ulcer                      | 314                          |
|  |                              | gastritis                  | 51, 212, 340, 402, 404       |
|  |                              | atrophic                   | 78                           |
|  |                              | chronic                    | 411                          |
|  |                              | tuberculous                | 408                          |
|  |                              | ulcerative                 | 191                          |
|  |                              | Gastro-duodenal fistula    | 212                          |
|  |                              | motility                   | 375                          |
|  |                              | Gastro-enteric stoma       | 313                          |
|  |                              | Gastro-enterology          | 241                          |
|  |                              | Gastro-enterostomy         | 153, 317                     |
|  |                              | Gastro-intestinal bleeding | 118                          |
|  |                              | section                    | 389                          |
|  |                              | Gastrojejunal ulcer        | 314                          |
|  |                              | Gastrojejunitis            | 314                          |
|  |                              | Gastrojejuno-colic fistula | 192, 195                     |
|  |                              | Gastrojejunostomy          | 314                          |
|  |                              | Gastroscope, flexible      | 414                          |
|  |                              | Gastrosopic examination    | 401                          |
|  |                              | study                      | 289                          |
|  |                              | technique                  | 48                           |
|  |                              | Gastroscopy                | 109, 149, 262, 315, 398, 410 |
|  |                              | Giardardi intestinalis     | 360                          |
|  |                              | Giardiasis                 | 253                          |
|  |                              | Glossitis                  | 350                          |
| Edema                                  | 189                          |                            |                              |
| Electrocardiogram                      | 295                          |                            |                              |
| Embolism                               | 348                          |                            |                              |
| Emetine therapy                        | 360                          |                            |                              |
| Endamoeba histolytica                  | 328                          |                            |                              |
| Endomyces                              | 201                          |                            |                              |
| Entameba histolytica                   | 359                          |                            |                              |
| Enteritis, prognosis in                | 87                           |                            |                              |
| Entero-anastomosis                     | 90                           |                            |                              |
| Enterobiasis                           | 257                          |                            |                              |
| Enterocolitis                          | 350                          |                            |                              |
| Enterograph                            | 376                          |                            |                              |
| Enzymatic activity                     | 98                           |                            |                              |
| Enzyme determinations                  | 186                          |                            |                              |
| Enzymes                                | 309                          |                            |                              |
| blood                                  | 160                          |                            |                              |
| Epinine                                | 36                           |                            |                              |
| Erepsin                                | 261                          |                            |                              |
| Ergosterol                             | 367                          |                            |                              |
| Ergotamine tartrate                    | 202, 301                     |                            |                              |
| Erosions                               | 411                          |                            |                              |
| Esophagopleural fistula                | 211                          |                            |                              |
| Esophagus                              | 211                          |                            |                              |
| Ewald meal                             | 364                          |                            |                              |
| Exomphalos                             | 383                          |                            |                              |
| Experimental pancreatic fistula        | 306                          |                            |                              |
| ulceration                             | 205                          |                            |                              |

|                                      |                         |                            |                    |
|--------------------------------------|-------------------------|----------------------------|--------------------|
| Glucose                              | 363                     | parasites                  | 34                 |
| Glycogen                             | 118                     | tuberculosis               | 215                |
| Granuloma                            | 87                      | Intubation technique       | 202                |
| Granulomatosis, lipophagic           | 55                      | Intussusception            | 210, 214, 259      |
| Gummata                              | 212                     | Irritable colon            | 245, 281           |
| Haemokonin                           | 395                     | Jaundice                   | 118, 342           |
| Halitosis                            | 79                      | obstructive                | 1, 6               |
| HCl                                  | 405                     | Jejunal diverticulitis     | 214                |
| Hemangioma                           | 214, 215                | ulcer                      | 193                |
| Hematemesis                          | 110                     | Joint hemorrhages          | 189                |
| Hematoma                             | 168                     | Juvenile diarrhea          | 253                |
| Hematuria                            | 118                     |                            |                    |
| Hemicellulose hydrogels              | 387                     | Keratotic papules          | 189                |
| Hemi-decerebration                   | 361                     |                            |                    |
| Hemorrhage                           | 110, 150, 314, 319, 348 | Laënnec's cirrhosis        | 116                |
| Hemorrhagic gastritis                | 314                     | Leiomyosarcoma             | 214                |
| Hemorrhoids                          | 247, 256                | Leishmaniasis              | 360                |
| Heparinized plasma                   | 2                       | Leucopenia                 | 330                |
| Hepatic disease                      | 1                       | Lignin                     | 387                |
| Hepatic ducts                        | 216                     | Lipemia                    | 2                  |
| Hepatic function                     | 82                      | Lipids of plasma           | 1                  |
| Hepatico-renal syndrome              | 348                     | Lipogranulomas             | 55                 |
| Hepatitis                            | 100                     | Lipomas                    | 215                |
| Heterotaxy                           | 217                     | Lipopenia                  | 2                  |
| Hiatus esophageal hernia             | 210                     | Lipophagic granulomatosis  | 55                 |
| Hidradenitis suppurativa             | 220                     | Liver, cirrhosis           | 35, 342            |
| High carbohydrate feeding            | 264                     | disease                    | 99                 |
| Hippuric acid                        | 51                      | function                   | 141, 183           |
| Hippuric acid test                   | 13, 183                 | function tests             | 13                 |
| Histaminase                          | 352                     | Liver-stomach concentrate  | 78                 |
| Histamine                            | 352, 367                | Lymphogranuloma venereum   | 215, 233, 237, 254 |
| Histaminic cephalalgia               | 352                     | Lymphoid tumors            | 213                |
| Histopathology, of gastritis         | 411                     | Lymphosarcoma              | 45, 213            |
| Hodgkin's disease                    | 210                     |                            |                    |
| Hookworm infestation                 | 247                     | Magnesium sulphate         | 162                |
| Hormodendrum                         | 201                     | Malabsorption              | 351                |
| Human feces                          | 200                     | of fat                     | 56                 |
| Hunger                               | 309                     | Malaria                    | 327                |
| Hydatid cysts                        | 217                     | Malarial dysentery         | 360                |
| Hydrochloric acid                    | 209                     | Malignant disease of colon | 250                |
| Hydrogels                            | 387                     | leiomyoma                  | 213                |
| Hydrolysate mixture                  | 350                     | Malnutrition               | 300, 314           |
| Hyperchlorhydria                     | 212                     | Malrotation                | 383                |
| Hypercholesterolemia                 | 1                       | Mann-Williamson dogs       | 173                |
| Hyperglycemia                        | 153, 363, 366           | ulcers                     | 166                |
| Hyperkeratotic skin papules          | 189                     | Marginal ulcer             | 314                |
| Hyperperistalsis                     | 216                     | Mecholyl                   | 202                |
| Hyperpyrexia                         | 348                     | Meckel's diverticulum      | 214                |
| Hyperthyroidism                      | 218                     | Melanosis coli             | 258                |
| Hypertrophic gastritis               | 212, 341, 401, 413      | Melena                     | 110                |
| Hypertrophy of sphincter choledochus | 216                     | Mesenteric pedicle         | 383                |
| Hypoglycemia                         | 151, 367                | Mesocolon                  | 313                |
| Hypoproteinemia                      | 2, 313                  | Metabolic disturbances     | 329                |
| Hypoprothrombinemia                  | 228, 422                | Metabolism                 | 357                |
| Hypotension                          | 330                     | Metaplasia of epithelium   | 149                |
| Hypothalamus                         | 358, 361                | Meulengracht regimen       | 150                |
|                                      |                         | Midgut, anomalies of       | 383                |
| Idiopathic ulcerative colitis        | 74                      | Milk                       | 189                |
| Ileal stoma                          | 74                      | Miller-Abbott tube         | 351                |
| Ileitis, non-specific                | 64                      | Minerals                   | 90                 |
| Ileocolostomy                        | 64                      | Molds                      | 200                |
| Ileostomy                            | 281, 351                | Monilia                    | 201                |
| Indeterminate fever                  | 181                     | Morphine                   | 202                |
| Inductorium                          | 361                     | sulfate                    | 37                 |
| Infections, anorectal                | 144                     | Motility of G.I. tract     | 268                |
| Infra-red photography                | 392                     | Movements of pancreas      | 76                 |
| Injectational therapy                | 256                     | Mucosa, gastric            | 149, 407           |
| Inositol                             | 268                     | redundant                  | 287                |
| Insomnia                             | 330                     | Mucus                      | 425                |
| Insulin                              | 363                     | Muscular twitching         | 137                |
| allergy                              | 352                     | Mysathenia gravis          | 211                |
| Internal abdominal herniae           | 216                     |                            |                    |
| Intestinal digestion                 | 114                     |                            |                    |
| disorders                            | 359                     | Nausea                     | 87, 151, 405       |
| hypermotility                        | 74, 75                  | Necrosis of liver cells    | 187                |
| obstruction                          | 177                     | Neosynephrin               | 36                 |

|                               |                         |                                 |              |
|-------------------------------|-------------------------|---------------------------------|--------------|
| Neurohypophysis               | 234                     | Physiologic dysfunction         | 315          |
| Neutral red                   | 109                     | Phytobezoar                     | 215          |
| New instruments               | 250                     | Picrolonate                     | 68           |
| Nicotinic acid                | 268                     | Pitoein                         | 295          |
| Night blindness               | 114, 118, 189           | Pitressin                       | 295          |
| Nitrites                      | 211                     | Pituitrin                       | 295          |
| Nitrogen                      | 351                     | Plasma, heparinized             | 2            |
| Nitrogen balance              | 74                      | Plasma lipids                   | 1            |
| Nitroglycerine                | 37, 202                 | Polyps                          | 248          |
| Non-specific ileitis          | 64                      | Porphyria                       | 43           |
| ulcerative colitis            | 229                     | Portal cirrhosis                | 58, 115      |
| Nutritional problems          | 309                     | hypertension                    | 118          |
|                               |                         | vein pattern                    | 392          |
| Oatmeal                       | 189                     | Porter-Vinson syndrome          | 211          |
| Obstructed peptic ulcer       | 321                     | Posterior gastro-enterostomy    | 193          |
| Obstruction                   | 314, 319                | pituitary extract               | 234          |
| duodenal                      | 45                      | Post-operative diarrhea         | 90           |
| of biliary duct               | 1                       | Potassium                       | 264          |
| Obstructive jaundice          | 1, 6, 100, 398          | Pregnancy                       | 258, 395     |
| Occult blood                  | 154                     | Pressure, intraduodenal         | 425          |
| Occurrence, familial, colitis | 147                     | Preventive methods              | 327          |
| Oddi, sphincter of            | 36                      | Proctocolitis                   | 215          |
| Oidium                        | 201                     | Proctoscopic cinematography     | 140          |
| Oil of peppermint             | 38                      | Propadrine                      | 36           |
| Old age                       | 157, 160                | Prostigmine                     | 38, 202, 211 |
| Oleum percomorphum            | 119                     | Protein                         | 90           |
| Omentopexy                    | 118                     | catabolism                      | 82           |
| Opium                         | 36                      | deficiency                      | 78           |
| Oral hippuric acid test       | 13                      | digest                          | 175          |
| Osmotic changes               | 366                     | Prothrombin                     | 419          |
|                               |                         | Pruritus                        | 255          |
| Palpitation                   | 151                     | of jaundice                     | 301          |
| P-aminobenzoic acid           | 268                     | Pseudobulbar palsy              | 285          |
| Pancreas                      | 303                     | Pseudo-diverticula              | 283          |
| movements of                  | 76                      | Pseudogastritis                 | 210          |
| Pancreatic disease            | 217                     | Psychic trauma                  | 358          |
| enzymes                       | 354                     | Pulmonary collapse              | 348          |
| insufficiency                 | 303                     | Purpura                         | 227          |
| lithiasis                     | 305                     | Pyloric obstruction             | 316, 321     |
| necrosis                      | 186                     | stenosis                        | 213          |
| secretion                     | 157, 160                | Pyramidal tracts                | 285          |
| Pancreatitis                  | 51, 119, 186, 217       | Pyridoxine                      | 268          |
| hemorrhagic                   | 428                     |                                 |              |
| in alcoholism                 | 428                     | Quinine                         | 327          |
| Papilloma                     | 216                     |                                 |              |
| Parasites                     | 327                     | Reaction, serum coagulation     | 129          |
| Parathormone                  | 367                     | Redundant gastric mucosa        | 287          |
| Parathyroidectomy             | 367                     | Regional enteritis              | 87           |
| Paratyphoid B infection       | 233                     | ileitis                         | 65, 214      |
| Parkinson syndrome            | 285                     | Rehfuß tube                     | 354          |
| Parkinsonism                  | 282                     | Remissions                      | 78           |
| Parotid duct obstruction      | 417                     | Resection, gastric              | 317          |
| Parotitis                     | 418                     | gastric subtotal                | 151          |
| Patent stoma                  | 315                     | of bowel                        | 88           |
| Paylov pouches                | 234                     | Retractile mesenteritis         | 217          |
| Pellagra                      | 29                      | Review, X-ray                   | 211          |
| Pellagrous dermatitis         | 118                     | Rheumatic vegetations           | 57           |
| Penicillium                   | 201                     | Riboflavin                      | 268          |
| Pepsin                        | 261                     | diet                            | 118          |
| Peptic activity               | 206                     | Roentgenological review         | 211          |
| ulcer                         | 151, 189, 245, 363, 404 | Rosenthal bromsulphthalein test | 13           |
| bleeding                      | 150                     | Russell bodies                  | 412          |
| ulceration                    | 212                     |                                 |              |
| Perforation                   | 410                     | Salts                           | 268          |
| of esophagus                  | 146                     | Salyrgan                        | 119          |
| of rectum                     | 256                     | Saponification number           | 56           |
| of ulcer                      | 397                     | Schistosomiasis                 | 360          |
| Peripheral neuritis           | 350                     | Secretion, gastric              | 234, 275     |
| Perirectal abscess            | 181                     | pancreatic                      | 157          |
| Peristalsis                   | 362                     | Secretin test                   | 68           |
| Peritoneal fusion             | 386                     | Serial bromsulphthalein test    | 13           |
| Pernicious anemia             | 29, 261, 404            | Serum amylase                   | 305          |
| Phagocytosis                  | 57                      | B. coli                         | 133          |
| Phenolphthalein               | 107, 292                | cholinesterase                  | 342          |
| Phlegmonous gastritis         | 212                     | coagulation                     | 129          |
| Phosphatase                   | 343, 367                | diastase                        | 160          |
| Photography, infra-red        | 392                     | lipase                          | 160          |
|                               |                         | sickness                        | 352          |



|                              |                    |  |                                  |
|------------------------------|--------------------|--|----------------------------------|
| Sexual maladjustments        | 188                | of esophagus                           | 211                              |
| Shock                        | 113, 348           | of gall bladder                        | 216                              |
| Sialodochitis                | 417                | of small intestine                     | 214                              |
| Siderophrenia                | 211                | of stomach                             | 213                              |
| Sleep                        | 137                | Typhus fever                           | 328                              |
| Smooth muscle tumors         | 213                | Tyrosin                                | 99, 350, 351                     |
| Sodium                       | 264                | Tyrosinemia                            | 100, 101                         |
| bicarbonate                  | 202                |  |                                  |
| sulfanilyl sulfanilate       | 237                | Ulcer, chronic                         | 338                              |
| Somogyi units                | 160                | experimental                           | 205                              |
| Sour stomach                 | 49                 | obstructed                             | 321                              |
| Spasms of esophagus          | 282                | resection for                          | 317                              |
| Sphenoid sinus               | 358                | Ulcerative colitis                     | 91, 133, 210, 247, 350, 356, 395 |
| Sphincter of Oddi            | 36, 40, 162        | chronic                                | 147                              |
| Spinach                      | 189                | idiopathic                             | 74                               |
| Spindle cell sarcoma         | 213                | Ulcerative gastritis                   | 191                              |
| Sprue                        | 29                 | Ulcer-bearing area                     | 276                              |
| Squash                       | 189                | Ultero-genesis                         | 358                              |
| Starvation                   | 2                  | Ulcers, cinchophen                     | 352                              |
| Steatorrhea                  | 57                 | Mann-Williamson                        | 166                              |
| Stenson's duct               | 418                | Urea                                   | 264                              |
| Stoma, gastro-enterie        | 313                | Urine extracts                         | 166                              |
| Stomach                      | 212                | Urobilinogen                           | 168                              |
| submucosal tumors of         | 289                | Urobilinuria                           | 168                              |
| test meals in                | 363                | Urticaria                              | 352                              |
| Stones, in common duct       | 52                 | Ultero-genesis                         | 358                              |
| Stovarsol                    | 360                | Ulcers, einchophen                     | 352                              |
| Streptococci                 | 356                | Mann-Williamson                        | 166                              |
| Strictures                   | 215                | Urea                                   | 264                              |
| Stricture of rectum          | 237                | Urine extracts                         | 166                              |
| Submucosal tumors of stomach | 289                | Urobilinogen                           | 168                              |
| Subphrenic abscess           | 217                | Urobilinuria                           | 168                              |
| Subtotal gastric resection   | 151, 317           | Urticaria                              | 352                              |
| Sucrose                      | 268                |  |                                  |
| tolerance tests              | 151                | Vagotomy                               | 362                              |
| Suction-irrigation           | 210                | Variees, of gall bladder               | 399                              |
| Sulfanilamide                | 144, 229, 259, 356 | Vasomotor rhinitis                     | 352                              |
| Superficial gastritis        | 412                | Ventriculin                            | 78                               |
| chronic                      | 341                | Vesiculo-postular eruption             | 357                              |
| Suppositories                | 144                | Vioform                                | 360                              |
| Survey, vitamin              | 188                | Virus                                  | 328                              |
| Sweet potatoes               | 189                | Vitamin A                              | 189                              |
| Syndrome, hepatico-renal     | 348                | B                                      | 90, 350                          |
| Syntropan                    | 202                | B <sub>2</sub>                         | 118                              |
| Syphilis                     | 191, 409           | B <sub>6</sub>                         | 118                              |
| of duodenum                  | 214                | B complex                              | 119                              |
| of esophagus                 | 211                | B deficiency                           | 75, 78, 218                      |
| of stomach                   | 212                | C                                      | 151, 406                         |
| Syphilitic cirrhosis         | 115                | D                                      | 191                              |
|                              |                    | E and K                                | 191                              |
|                              |                    | K deficiency                           | 227                              |
|                              |                    | preparations                           | 312                              |
| Tattooing                    | 255                | survey                                 | 188                              |
| Teeth                        | 189                | Vitamins                               | 90, 309, 357                     |
| Test, hippuric acid          | 183                | Vitelline duct                         | 383                              |
| Test meals                   | 363                | Volatile fatty acids                   | 389                              |
| Test, secretin               | 68                 | Volvulus                               | 214, 258, 316                    |
| Tetany                       | 314                | cecal                                  | 177                              |
| Thiamine hydrochloride       | 268                | Vomiting                               | 87, 323, 330                     |
| Thrombo-ulcerative colitis   | 147                |  |                                  |
| Thyroid disease              | 218                | War, and gastro-enterology             | 241                              |
| Töepfer's reagent            | 107                | Wartime nutrition                      | 309                              |
| Total acidity                | 355                | War wounds of colon                    | 257                              |
| Toxemia                      | 314                | Wassermann reaction                    | 213                              |
| Tracheo-esophageal fistula   | 211                | Water brush                            | 49                               |
| Traction bands               | 384                | Water, secretion of                    | 416                              |
| Transposition of viscera     | 217                | Weakness                               | 151, 330                         |
| Trasentin                    | 37                 | Weltmann reaction                      | 132                              |
| Treparsone                   | 360                |  |                                  |
| Trichobezoar                 | 198                | Xerophthalmia                          | 189                              |
| Triparsamide therapy         | 191                | X-ray diagnosis, in pancreatic disease | 305                              |
| Tropical sprue               | 261                | X-ray studies                          | 313                              |
| disease                      | 327                |  |                                  |
| Trypsin                      | 68, 70, 261        | Yeast                                  | 406                              |
| Tsetse flies                 | 329                | Yellow fever                           | 328                              |
| Tuberculosis                 | 87, 254, 407       |  |                                  |
| intestinal                   | 404                |  |                                  |
| pulmonary                    | 404                |  |                                  |
| Tumors of duodenum           | 214                | Zweiback                               | 364                              |

